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BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 14 1954

# CORTISONE IN ULCERATIVE COLITIS

## PRELIMINARY REPORT ON A THERAPEUTIC TRIAL

BY

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**With the co-operation of Professor R. E. TUNBRIDGE and Dr. G. WATKINSON (Leeds), Dr. F. AVERY JONES and Dr. RICHARD DOLL (North-west London), Professor T. L. HARDY and Dr. C. R. ST. JOHNSTON (Birmingham), Dr. W. I. CARD and Dr. MAXWELL WILSON (Edinburgh), and Sir JOHN TAYLOR (Medical Research Council)**

There are conflicting reports of the value of corticotrophin (A.C.T.H.) and cortisone in non-specific ulcerative colitis. The disease is so variable in its severity and course that a large-scale trial in which cortisone-treated and control groups are compared has been carried out to decide the issue. This therapeutic trial originally began in the Oxford region in March, 1952, with the help of the Medical Research Council, who agreed to supply cortisone. However, physicians in other regions were interested in the same subject, and the outcome was that four other regions arranged to take part in the trial, working to the same plan as had been evolved for the Oxford region. The other regions concerned were Leeds, North-west London, Birmingham, and Edinburgh.

### The Plan

Full details of the plan will be given in the final report, and only some salient features are now mentioned. The trial was a "blind" one in that dummy treatment was given to approximately half the patients, and the physician in charge of the patient did not know whether cortisone or a dummy was issued. It was judged that if the physician proceeded on the assumption that every patient might be receiving potent cortisone, and if he also had the right to stop treatment at any time he considered it likely to be doing harm, such a blind trial was justified because of the greater value of its results. Other conventional forms of medical treatment could be used in addition to the specific therapy at the discretion of the physician in charge of the patient.

*Dosage.*—During the first half of the trial, covering 107 patients, cortisone was given orally for a period of six weeks. The dosage was 100 mg. a day, given as 25 mg. before each of the three main meals and 25 mg. at bedtime. This dosage could be reduced after two weeks to a lower maintenance dose of 50–75 mg. daily. The cortisone was tailed off to nothing in the final week of treatment. During the second half of the trial the physician in charge of a case could increase the dose up to 300 mg. a day and the course could be prolonged up to three months. Potassium citrate in a dose of 1 g. four times a day was given throughout the course of treatment. Close watch was kept for electrolyte disturbances which might occur both from the disease processes and from the action of cortisone. Blood electrolyte estimations and electrocardiograms were to be carried out on every patient.

*Selection of Cases.*—Patients in their first attack and those in a definite relapse were used for the trial. The physicians were instructed not to include patients in whom the disease was causing only very mild symptoms. In other words, the trial was to be confined to patients who would normally be expected to require at least six weeks' treatment in hospital. Patients with regional colitis or ileitis were not included. Patients who suffered from the following diseases in addition to ulcerative colitis were also not included: proved chronic peptic ulcer; hypertension; pulmonary tuberculosis; any other severe illness likely to influence the prognosis greatly. A chest *x*-ray examination was to be done in all cases to exclude pulmonary tuberculosis; and a barium-meal examination was to be made if the physician thought it desirable.

*First Attacks and Relapses.*—These were handled separately in the design of the master sheets because previous work suggested that their prognosis might be different. Physicians were asked to classify the illness as a relapse when the patient had previously had an attack of bloody diarrhoea without good evidence of its being due to a specific infection such as bacillary dysentery. In patients with the chronic continuous form of the disease the case was classified as a relapse if the symptoms had lasted more than two years.

### Results

A total of 213 patients received treatment. Of these, three have been rejected from the analysis of results for the following reasons: one patient proved to be suffering from carcinoma of the colon, one had had a colostomy, and in the third the records were inadequate. Of the remaining 210 patients, 109 received cortisone and 101 received the dummy preparation.

#### Dosage

The actual dosage of cortisone used with the 109 patients who received a potent preparation was as follows:

| | | |
|---|---|---|
| 100 mg. a day for six weeks | 38 | patients |
| 100 mg. a day for two to three weeks, followed by smaller doses of 50–75 mg. a day | 38 | ,, |
| Doses of 100 mg. and more | 17 | ,, |
| Therapy abandoned before completion | 16 | ,, |

The patients in whom therapy was abandoned before completion of the six weeks period fell into two

categories: first, those who were deteriorating on treatment; secondly, some of the patients who went into a remission rapidly after beginning cortisone.

### Effect of Treatment on Clinical State

The effect of treatment was assessed by placing patients into three categories at the end of six weeks' treatment. In the majority this was at the *conclusion* of their treatment; a minority during the second half of the trial received treatment for a longer period than six weeks, and for convenience in assessing the results their condition at the end of six weeks has likewise been taken. In some patients the specific therapy was abandoned before six weeks had passed, as noted above, and their condition has been assessed at the time when treatment was abandoned. The three clinical categories were as follows:

*Clinical Remission.*—One or two stools a day without blood. No fever. No tachycardia. Haemoglobin normal or returning towards normal. E.S.R. normal or returning towards normal. Gaining weight. (To be included in this category the patient was expected to show all the above features. In the great majority of the cases all these data were included in the records, but in some the data for haemoglobin, E.S.R., or weight were incomplete. In such cases all the available data had to conform to this schedule.)

*No Change or Worse.*—Self-explanatory.

*Improved.*—All intermediate cases.

The results for the whole group are shown in Table I and Fig. 1, which demonstrate that the patients receiving cortisone enjoyed a clear-cut advantage over the patients on a dummy preparation. Thus about two out of every five patients on cortisone therapy were in clinical remission at the end of six weeks' treatment, compared with less than one out of every six patients receiving the inert therapy.

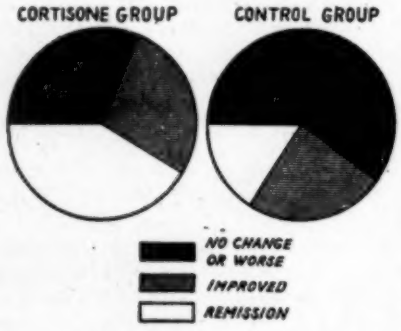


FIG. 1.—Effect of treatment — whole series.

TABLE I.—*Effect of Treatment on Whole Series*

| Clinical State at End of Treatment | Cortisone Group | Control Group |
|---|---|---|
| Remission .. .. .. | 45 (41·3%) | 16 (15·8%) |
| Improved .. .. .. | 30 (27·5%) | 25 (24·8%) |
| No change or worse .. | 34 (31·2%) | 60 (59·4%) |
| Total .. .. | 109 (100%) | 101 (100%) |

$\chi^2 = 21{\cdot}2$. n = 2. $P < 0{\cdot}001$.

Table II and Fig. 2 show the results separately for patients admitted in their first attack of the disease and patients admitted in a relapse. In each case the cortisone group shows results which are significantly better than those of its control group. The beneficial effect of cortisone appears to be particularly well marked in first attacks of the disease. Past experience has shown that first attacks are in general more dangerous than relapses, and this relationship holds good for the control groups. By contrast, among the patients treated with cortisone those in their first attack have fared somewhat better than those in relapse.

TABLE II.—*Effect of Treatment in First Attacks and Relapses*

| | First Attacks | | Relapses | |
|---|---|---|---|---|
| | Cortisone Group | Control Group | Cortisone Group | Control Group |
| Remission .. | 19 (42·2%) | 5 (13·2%) | 26 (40·6%) | 11 (17·5%) |
| Improved .. | 16 (35·6%) | 6 (15·8%) | 14 (21·9%) | 19 (30·2%) |
| No change or worse .. | 10 (22·2%) | 27 (71·1%) | 24 (37·5%) | 33 (52·4%) |
| Total .. | 45 (100%) | 38 (100%) | 64 (100%) | 63 (100%) |
| | $\chi^2 = 20{\cdot}1$, n = 2, $P < 0{\cdot}001$ | | $\chi^2 = 8{\cdot}25$, n = 2, $0{\cdot}02 > P > 0{\cdot}01$ | |

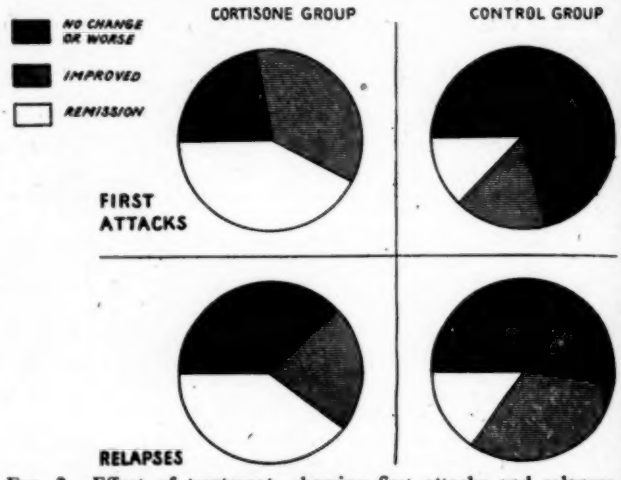


FIG. 2.—Effect of treatment, showing first attacks and relapses separately.

### Sigmoidoscopy and Barium Enema

Unfortunately the data with respect to sigmoidoscopy and barium enema findings are incomplete. All patients had one or other of these examinations made before treatment began, and the majority had both, as part of the diagnostic criteria for admitting patients to the trial, but a large number of patients did not have these examinations repeated at the end of treatment. Some physicians are reluctant to carry out these examinations once the diagnosis has been established for fear of provoking recurrence, and others may have failed to appreciate their desirability as part of the assessment of results.

With respect to sigmoidoscopic findings, there were 120 patients who were examined at the end of their course of treatment, so that comparison can be made with the sigmoidoscopic appearances at the beginning. The results are shown in Table III. Of the 120 patients, there were 63 in the cortisone group, and 57 in the control group. The cortisone sample contains approximately three times as many patients whose sigmoidoscopic findings at the end of treatment were normal or near normal. (The findings were classed as near normal when slight hyperaemia or slight granularity was the only abnormal finding.) Comparison of these two samples shows that the differences between them would be expected by chance about once in 50 times, so they may be deemed to be significantly different. If we make the assumption that these samples of the cortisone and control groups are equally representative of their parent groups we may conclude that the patients treated with cortisone were more likely to show sigmoidoscopic improvement than were the patients of the control group.

TABLE III.—*Sigmoidoscopic Appearances in 120 Patients Examined at the End of Treatment*

| | Cortisone Group | Control Group |
|---|---|---|
| Normal or near normal .. | 19 | 6 |
| Improved .. .. .. | 14 | 12 |
| No change or worse .. | 30 | 39 |
| Total .. .. | 63 | 57 |

$\chi^2 = 7{\cdot}81$. n = 2. $P \simeq 0{\cdot}02$.

Data with respect to barium enema are even less adequate than those for sigmoidoscopy, because only 51 of the 210

patients had a barium enema examination carried out at the end of treatment. The results for this sample are shown in Table IV. Only a small proportion of the sample show

TABLE IV.—*Barium Enema Findings in 51 Patients Examined at the End of Treatment*

| | Cortisone Group | Control Group |
|---|---|---|
| Normal .. .. .. | 2 | 2 |
| Improved .. .. .. | 10 | 4 |
| No change or worse .. | 14 | 19 |
| Total .. .. | 26 | 25 |

normal findings at the end of treatment, which is not surprising, as it is common experience that the changes found on barium enema examination in this disease may persist long after a complete clinical remission. A bigger proportion of patients show some improvement in the barium enema findings, although these have not returned to normal; such improvement was more commonly found in the patients of the cortisone group. So far as we are able to deduce anything from such a small sample of the total number of patients, the changes in the barium enema findings are in the same direction as the clinical response—namely, that the cortisone group do better than the control group.

### Recurrences after Stopping Therapy

A small number of patients treated with cortisone relapsed shortly after the end of treatment. For example, during the first half of the trial covering 107 patients there were 57 patients treated with cortisone; of 27 of these patients who were in remission at the end of treatment, 2 relapsed shortly afterwards; and of 18 who were "improved" during the treatment, there were 2 who had an exacerbation when it ended. By contrast there were no patients among the 50 control cases who went into a definite relapse when treatment stopped. (The liability to relapse at the end of treatment is less easy to determine for the patients in the second half of the trial, when treatment could be continued for longer than the six-weeks period at the discretion of the physician in charge.)

The following comments are worth making about this finding. The relapses among the cortisone-treated group suggest that the cortisone was holding the activity of the disease in check. It is likely that some patients will require continuous treatment to maintain their improvement, but this point has not been studied in the present trial. In any event, the frequency of relapse on stopping treatment is not high enough to alter the conclusion that cortisone is beneficial.

### Complications

A variety of complications occurred during the trial; these will be dealt with in detail in the final report. For the moment it is worth recording that the only two cases of perforation of the bowel occurred among the patients of the control group. There was one case of massive haemorrhage from the bowel in a patient receiving large doses of cortisone.

### Ileostomy

Twenty-three patients were submitted to ileostomy during or not long after their course of treatment, because of failure of medical measures. Among the cortisone group there were 9 patients (8.3%) who were treated by ileostomy during the trial period or within the next few weeks, compared with 14 patients (13.9%) of the control group.

### Deaths

There were 15 deaths during treatment or during the next few weeks. Five of these were among the cortisone-treated group, a mortality of 4.6%, and 10 among the control group (9.9%). Seven of the deaths occurred among the 23 patients who were submitted to ileostomy, 2 of them being in the cortisone-treated group and 5 in the control group.

## Discussion

There are already many reports of the treatment of ulcerative colitis with cortisone and A.C.T.H. (Dearing and Brown, 1950; Elliott and others, 1951; Halsted and others, 1951; Kirsner and Palmer, 1951; Machella and Hollan, 1951; Rossmiller and others, 1951; Bekaert and Vuylsteek, 1952; Brown and McAuley, 1952; Gray and others, 1952). Most of the authors have noted considerable subjective improvement, with gain in appetite and reduction of diarrhoea. Objective improvement has been less often observed, but in those patients in whom the diarrhoea was most diminished sigmoidoscopic examination of the colon showed a decrease in inflammatory reaction. However, in none of these reports was there a formal trial in which some patients received therapy and some did not. In consequence it is difficult to judge from them how beneficial are the actions of A.C.T.H. and cortisone, particularly when it is borne in mind that ulcerative colitis is prone to show remissions even in the absence of specific therapy.

The present study deals with a considerable number of patients, who were allotted in a random order to treatment with cortisone or a dummy preparation without the physician in charge of the patient being informed of the nature of the treatment, unless such information became necessary as a result of a grave emergency. The results show that, as judged by ordinary clinical criteria, cortisone was undoubtedly beneficial in increasing the chance of remission. The effect was particularly striking in patients suffering from their first attack of the disease. It is known from previous observations (Rice-Oxley and Truelove, 1950) that first attacks are usually more serious than relapses, and this relationship holds true in the present study for the patients of the control group. By contrast, in the cortisone group, patients in their first attack fared somewhat better than those suffering from relapses.

It is unfortunate that a large number of patients were not examined again by sigmoidoscopy and barium enema at the end of treatment in order to permit comparison with the findings at the beginning. Sigmoidoscopy was carried out at the end of treatment in 63 patients in the cortisone group and 57 in the control group. Findings were significantly better in the cortisone group than in the control group, so that if we make the assumption that these samples were equally representative of the two parent groups we may conclude that cortisone exerts a beneficial influence on the disease when judged by sigmoidoscopy. The barium enema findings are less adequate, as this examination was made in only 51 of the 210 patients at the end of treatment, but within this small sample such differences as exist are in favour of the cortisone group.

The decision to submit a patient to ileostomy because medical treatment is failing constitutes a yardstick of the efficacy of medical measures. Likewise the number of patients dying during the trial period of treatment or within the next few weeks may be taken as a criterion. In each case the cortisone group compares favourably with the control group. Although the differences between the two groups are not statistically significant they may reasonably be regarded as reinforcing the previous conclusion that cortisone is beneficial.

Thus the criteria used—namely, the overall clinical picture, changes in sigmoidoscopic appearances, changes in the barium enema findings, resort to surgery because of failure of medical treatment, and early death—all point in the same direction, that cortisone confers benefit upon patients with an acute attack of ulcerative colitis.

Cortisone has its own dangers, which require evaluation. Halsted and others (1951), in treating 15 patients suffering from ulcerative colitis with A.C.T.H., had one patient who developed a perforated duodenal ulcer, one a coronary thrombosis, and one a massive haemorrhage followed by perforation. Tulin and others (1952) record that among 17 patients with ulcerative colitis treated with A.C.T.H. three developed peritonitis, from which one patient died; they believe that this agent is too dangerous to use in the acute

fulminating type of ulcerative colitis. Pessel and others (1953) report a fatal case of multiple bowel perforations and peritonitis occurring during treatment with A.C.T.H. It is therefore interesting to note that in the present study the only two cases of perforation of the bowel occurred in patients of the control group. One patient who was receiving large doses of cortisone had a massive haemorrhage from the bowel. Other less serious complications were fairly frequent in both the cortisone and the control group, and will be discussed in detail in the final report.

We do not, as yet, know whether the patients treated with cortisone will show any lasting benefit over the subsequent course of time. A small number of the patients treated with cortisone relapsed shortly after the cessation of treatment, but not enough to alter materially the general picture of its beneficial effects. We are attempting to follow the long-term progress of all patients who have been included in the trial, so that this point may eventually become clear. It is already known that some patients may relapse and need further courses of treatment in the future. It seems likely that some patients will require continuous treatment with cortisone to maintain their improvement, but the efficacy of long-continued treatment remains to be determined.


### Summary

Preliminary results are given of a therapeutic trial of cortisone in non-specific ulcerative colitis carried out by the co-operation of physicians in five hospital regions.

Of the 210 patients reported, 109 were treated with cortisone, the usual dose being up to 100 mg. a day for six weeks, and 101 received a dummy preparation.

As judged by the overall clinical response to treatment, the cortisone group enjoyed a clear advantage over the control group. Cortisone appeared to be particularly beneficial in first attacks of the disease.

Such data as exist on the changes in sigmoidoscopic and barium enema appearances between the beginning and end of treatment are in favour of the cortisone group.

Although neither difference is statistically significant, resort to ileostomy because medical treatment was failing, and death during the period of treatment or during the next few weeks, were both more common among the patients in the control group.

It is concluded that cortisone exerts a beneficial influence on the outcome of an acute attack of ulcerative colitis.


We wish to thank the many physicians who have taken part in the trial; their names will be published in the final report. The trial would have been impossible without the help of the Medical Research Council, who made available the cortisone used, met part of the clerical expenses, and provided facilities for meetings. Messrs. Merck kindly made a gift of cortisone and identical control tablets for a substantial part of the trial. We are indebted to the following pharmacists, who were responsible for the issue of cortisone and the dummy preparation within their regions: Mr. W. Trillwood (Oxford), Mr. N. W. Blacow (Leeds), Miss B. Boshell (N.W. London), Mr. E. Speakman (Birmingham), and Dr. G. Perrins (Edinburgh).


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# SOME OBSERVATIONS ON THE TREATMENT OF ULCERATIVE COLITIS WITH A.C.T.H.


BY

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Ulcerative colitis is a disease of unknown aetiology. Like many diseases the cause of which remains obscure, the aetiological factors are probably multiple, and the occurrence of the disease depends on their coincidental happening in a predisposed subject. Psychological factors undoubtedly play some part, while when the abnormal state of the mucous membrane is established, secondary infection is important. Little else can be said with certainty to be known of the cause of this disease. Treatment is confined either to general supportive measures with rest, diet, and blood transfusion, the correction of electrolyte balance in severe cases, and the treatment of secondary infection with antibiotics, on the one hand, or by ileostomy with or without colectomy on the other. Handling of psychological difficulties on common-sense lines is sometimes helpful, but formal psychotherapy is seldom indicated.

### The Literature

The introduction of A.C.T.H. and cortisone has led to their trial by many workers in America on patients with ulcerative colitis. The fact that this disease is occasionally complicated by arthritis raised the question whether cortisone might have an effect whether or not joint changes were present (Dearing and Brown, 1950). Rather different conclusions have been reached by different workers, but the majority have found that A.C.T.H. and cortisone have some effect on this disease. Dearing and Brown treated one case with both ulcerative colitis and arthritis with cortisone, 50 mg. twice daily intramuscularly for 35 days, with complete symptomatic relief of the colitis after a few days and recovery of the joints after four weeks. This was not accompanied by any objective improvement in the bowel, but subjective relief persisted for seven months. Two further cases with ulcerative colitis showed no response at all, while a fourth case showed temporary improvement on two occasions with courses of cortisone, but no change later after a course of A.C.T.H. Rather more favourable results were recorded by DuToit and Bauer (1950) in two cases, by Gray *et al.* (1950) in one case, and by Kirsner *et al.* (1950) in 11 cases treated with A.C.T.H. of which 9 responded. In five cases treated with cortisone by Kirsner *et al.* (1950) four showed some change, but in two of these it produced less benefit than A.C.T.H. had done previously.

Gray *et al.* (1951) treated six severe chronic cases in an acute phase which had failed to respond to a control period of medical management over one to four months. Doses of 20 to 40 mg. of A.C.T.H. six-hourly for four to eight weeks were used, with gradual reduction over a period of five to seven days at the termination of treatment. Five of the six patients experienced a dramatic

remission. Euphoria, increased appetite, disappearance of fever, and a fall in the sedimentation rate were noticed almost at once. Improvement in the stools occurred within a week, and a return to normal within two weeks. Whereas clinical improvement was evident within two weeks, objective evidence of healing on sigmoidoscopy took three to four weeks. One patient with a 23-year history and scarring of the whole colon did not respond. Relapses occurred in all but two patients from two to nine months after stopping treatment, but these responded satisfactorily to a second course of A.C.T.H. or cortisone. Two cases with regional enteritis showed improvement with A.C.T.H.

Halsted *et al.* (1951a) treated nine cases with A.C.T.H. with marked clinical improvement in two, slight improvement in two, and little or no change in five. The patients who did not respond showed some improvement in appetite and well-being. The two patients who improved most received relatively little hormone, and had had the disease for years. The *x*-ray changes were, however, less extensive than in the others. The same workers (Halsted *et al.*, 1951b) treated 15 patients, using the smallest dose of A.C.T.H. which appeared to have a beneficial clinical effect. Three cases had a sustained remission. Twelve cases relapsed soon after A.C.T.H. was stopped. Of these, six had shown some definite objective evidence of improvement, while six had merely subjective improvement. Five cases were also given cortisone at some stage. These authors are unable to draw any conclusions, but feel that cortisone is less effective than A.C.T.H. A larger series of 33 cases were treated by Elliott *et al.* (1951). Using 100 to 120 mg. of A.C.T.H. daily, they found a fall in temperature in two to three days, while there was an immediate improvement in appetite and euphoria. Of their 33 cases, 21 benefited materially, but 12 of them have relapsed.

Kirsner and Palmer (1951) treated 40 patients. The dosage varied, but was usually 20 or 25 mg. of A.C.T.H. six hourly, and the duration of treatment was over three weeks in 35 cases and over 30 days in 23 of them. They found that some beneficial effect was produced in 36 of the 40 cases, and that the clinical response was good in 27. Remissions were gradual in 12 cases and prompt in 24. In six cases faecal impaction developed, and in one case no bowel movement occurred for 26 days, although the patient remained in excellent health. They state that the clinical improvement was no more complete than has been observed previously with other treatment, but it was much more rapid. They mention the voracious appetite of many patients and the high daily calorie intake. Only four cases failed to show any response. Usually three to four weeks elapsed before there was definite evidence of proctoscopic improvement. The period of observation was less than a year in all but nine, but at the time of writing 15 cases had had a sustained remission and 20 had relapsed. One patient unaccountably committed suicide. In 14 of the relapsed cases the relapse was milder than the original attack, but in six it was of the same severity. Of the 38 surviving cases the disease was less severe in 27 after discontinuing A.C.T.H., notwithstanding relapses, while in 11 it was unchanged. The majority have resumed a useful life. Several cases received repeated courses. They concluded that A.C.T.H. does not cure ulcerative colitis, but often induces striking remission of the disease.

Machella and Hollan (1951) treated three cases of typical ulcerative colitis and three cases of regional enteritis with or without involvement of the proximal colon with a ten-day course of cortisone. Improvement followed later, but relapse occurred in five of the six. The improvement was most dramatic in the cases of regional ileitis, and particularly in two patients who were critically ill. Gray *et al.* (1952) report the follow-up of eight cases treated with fairly prolonged courses of A.C.T.H. and/or cortisone. In five of six acute cases a satisfactory remission occurred, as it did in two cases with chronic intractable diarrhoea. The one patient who failed to respond to treatment had a 23-year history, had multiple strictures and fistulas, and was in an acute exacerbation of the disease. Brown and McAuley (1952), using cortisone, treated nine patients, who between them received eleven courses. They stress the need for larger doses and a more prolonged course than that usually used by previous workers. They obtained good results in seven of their nine cases, of which three were acute and four were chronic cases in exacerbation, but two chronic cases did not respond.

Wirts *et al.* (1954) treated 40 patients with A.C.T.H., of whom 8 showed an excellent response, 14 a good response, and 6 only a fair response. The patients improving most were those who had widely spaced exacerbations with periods of complete remission. The optimum dose was found to be 20 mg., given by an eight-hour intravenous drip, daily for three weeks. Fifteen of these cases were followed for two and a half years, the remainder for shorter periods. Sixteen patients relapsed—four within one to six weeks, and the others after 12 to 18 months. All these responded to further treatment with A.C.T.H., but in later relapses the response was less prompt and less complete. In these cortisone was considered to be helpful.

The general conclusion reached by most of these workers is that A.C.T.H. and cortisone have an effect on appetite and produce a feeling of well-being in nearly every instance, usually accompanied by a gain in weight. These changes begin to occur almost at once, and are of themselves probably of benefit in ulcerative colitis. In those whose recovery starts with the administration of A.C.T.H., improvement in the stools takes longer to occur, while the colonic mucosa may take several weeks to return to normal or near normal. Cases are mentioned in which the clinical manifestations appear to be held in abeyance, although the appearance of the mucous membrane remains unchanged and relapse occurs at once after stopping the A.C.T.H. Several workers note that the more acute the disease the more likely it is to respond to A.C.T.H. or cortisone, and that little hope of benefit can be expected in chronic cases. Most conclude that A.C.T.H. has a place in the management of the disease. The only disagreement with this is by Redish (1951), who used much smaller doses of cortisone in seven cases, and found a negligible effect.

### Harmful Effects Noted

Harmful effects from the treatment have been mentioned in only a few instances. Tulin *et al.* (1952) report that among 17 patients with ulcerative colitis treated with A.C.T.H. a localized perforation of the bowel developed in one and an acute perforation with peritonitis in two. They note that the symptoms and signs of peritonitis were not suppressed as has been mentioned by others. Beck *et al.* (1950), for example, report the occurrence of peritonitis during the administration of A.C.T.H. in which many of the classical signs were absent. Pain and disappearance of peristaltic sounds were noted in two cases, but there was no fever, leucocytosis, or abdominal rigidity, and the pulse was normal. One of these was a case of Hodgkin's disease and the other of periarteritis nodosa. In one case (Gray *et al.*, 1952) a silent perforation of the colon with subphrenic abscess formation occurred without any of the classical signs and without apparently affecting the course of the ulcerative colitis, which had gone into remission while being treated with A.C.T.H. Halsted *et al.* (1951b) in their series had one case of perforation of the colon and one of perforation of the duodenum, the latter being in a patient with ulcerative colitis who had a past history of duodenal ulcer, but

had had no symptoms from it for three years prior to the start of A.C.T.H. treatment. The danger of using A.C.T.H. in patients with a past history of peptic ulcer is in any case now well known. Massive haemorrhage in patients with ulcerative colitis treated with A.C.T.H. has been reported three times (Hillemand and Gilbrin, 1951; Halsted *et al.*, 1951b; Wirts and Carroll, 1952). Various other side-effects, as seen in the treatment of any condition with A.C.T.H., were noted by some authors.

### Present Investigation

Fourteen cases have been treated during the past two and three-quarter years. It has not been practicable with the number of cases available to attempt a controlled experiment. In any case, when many of the patients were receiving four injections a day over a long period, it would hardly have been reasonable to subject a parallel group of cases to injections of an inert substance for the same length of time. Moreover, with A.C.T.H. a blind trial would not have been possible, as such a potentially dangerous substance, to which the individual response of patients varies so markedly, could not be used without the physician in charge knowing exactly what was being given. Although no definite conclusion can be drawn from the number of cases treated, it was thought that our experience with this small series of cases might be of interest to others.

The patients treated were all moderately or severely ill, and with two exceptions had been so for more than six months. None of them was showing any signs of making a spontaneous recovery, in spite of routine treatment, when A.C.T.H. was started Some had been ill for several years; details of the duration of illness, together with the previous course it had run, are given in the Table. Cases are described as severe when there was serious constitutional disturbance with a considerable degree of fever and very acute inflammatory changes in the mucosa. They were classed as moderate when there was less marked but definite constitutional disturbance with some fever. Usually in these cases there were less acute changes in the mucosa, but in some it was very acutely inflamed at some stage. In the present state of knowledge there does not seem to be any point in attempting to subdivide these cases further. In all of them there was evidence of involvement of the left half of the colon and rectum, and in seven there was necropsy, operative, radiological or clinical evidence that the whole colon was involved. Judging from the history, four of the cases appeared to have started as a proctitis.

All were straightforward cases of ulcerative colitis with the exception of Case 8, in which there had previously been a resection of part of the small intestine and the right half of the colon for regional ileitis which also involved the lower end of the right colon. The remainder of the patient's colon was at that time seen to be normal at operation, and sigmoidoscopy was also normal, but about a year later diarrhoea developed, and sigmoidoscopy showed the typical changes of ulcerative colitis in the lower bowel. Only two of the cases (Nos. 3 and 13) had had what appeared to be complete remissions, so far as could be judged from the history. Some of the others had run a course which fluctuated considerably, but had never been completely free of symptoms. In only two cases (Nos. 3 and 13) could it be said that a definite relapse was being treated. All the others had been chronically ill in varying degree from the onset of the trouble.

### General Management

The diagnosis was confirmed in all cases by sigmoidoscopy, or, if the inflammation was severe, by proctoscopy only. Examination by barium enema was made in those cases in which it was thought it would not be harmful, and in some instances had been made before the exacerbation of symptoms for which the patient had been admitted. Routine investigations included microscopical and bacteriological examination of stools, chest *x*-ray examination, blood count, sedimentation rate, plasma proteins, liver-function tests, and, before and during A.C.T.H. treatment, serum electrolyte and urinary 17-ketosteroid estimations.

The patients all received the usual dietary and general treatment, including a high-protein, high-calorie, low-residue diet with extra vitamins, blood transfusions given with the aim of keeping the haemoglobin at 100%, symptomatic measures for the control of diarrhoea, and sedatives as necessary. The possibility that psychological factors might be important was always considered, and any obvious problems were discussed with the patient on common-sense lines.

### Method of Treatment

When this investigation was started no information was available regarding the best method of administering A.C.T.H. for this disease. Cases were treated either with soluble A.C.T.H. every six hours or with A.C.T.H. gel once daily. In no case was A.C.T.H. given intravenously. In the first few cases the dose was worked up gradually, increasing every three or four days, to a maximum of 25 mg. of soluble A.C.T.H. every six hours, or 40 mg. of A.C.T.H. gel daily. When some experience had been gained it was customary to start with a dose of 15 mg. soluble A.C.T.H. six-hourly, or 20 mg. A.C.T.H. gel daily, and increase if necessary. It was aimed at giving a dose which had

*Summary of Results*

| No. | Age | Sex | Duration of Illness | Severity and Previous Course | Max. Dose of A.C.T.H. | Total Dose of A.C.T.H. | Duration in Days | Duration of Follow-up | Result |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | F | 9 years | Moderate; chronic; fluctuating | mg. 15×4 (sol.) | mg. 2,320 | 48 | 2¼ years | Said to be recovered |
| 2 | 36 | F | 3 „ | Severe; chronic; 1 partial remission for 1 year | 25×4 (sol.) | 3,400 | 45 | 2¼ „ | Recovered |
| 3 | 62 | F | 3 „ | Severe; relapsing; fulminating relapse | 25×4 (sol.) | 2,680 | 41 | — | Transient improvement; died later |
| 4 | 35 | M | 18 „ | Moderate; chronic; fluctuating | 20×4 (sol.) | 860 | 13 | 21 months | Slight maintained improvement |
| 5 | 28 | M | 1 year | Severe; chronic. Became fulminating | 25×4 (sol.) | 2,120 | 34 | — | Transient improvement; ileostomy and colectomy later. Subsequently died |
| 6 | 34 | F | 2 months | Moderate; acute | 20×4 (sol.) | 1,580 | 27 | 17 months | Recovered |
| 7 | 20 | F | 3 years | Severe; chronic; fluctuating | 15 (gel) | 205 | 20 | 1¼ years | Recovered. One relapse since, lasting two weeks |
| 8 | 25 | M | 10 months | Severe; chronic; previous ileitis | 20×4 (sol.) | 1,345 | 24 | 14 months | Slight maintained improvement |
| 9 | 44 | F | 1 year | Severe; chronic | 30 (gel) | 660 | 22 | 10 „ | Transient improvement. Ileostomy and colectomy later |
| | | | | | 40 „ | 1,385 | 68 (not every day) | | |
| 10 | 21 | F | 13 months | Moderate; chronic | 25×4 (sol.) | 1,700 | 20 | 1 year | Recovered |
| 11 | 35 | F | 8 „ | Moderate; chronic | 30 (gel) | 740 | 31 | 11 months | „ |
| 12 | 22 | F | 7 „ | Severe; chronic | 40 „ | 1,160 | 48 | 10 „ | „ |
| 13 | 27 | M | 2½ years | Moderate; relapsing | 30 „ | 675 | 33 | 10 „ | Much improved |
| | | | | | 30 „ | 785 | 27 | | |
| 14 | 40 | F | 3 months | Severe; acute | 30 „ | 1,025 | 56 | 5 „ | Slight improvement |

a definite stimulating effect, this dose to be given until improvement appeared to be well established. It was, of course, a much more difficult matter to decide on the correct dosage than in a disease like rheumatoid arthritis, in which treatment can be observed to produce a dramatic effect within a few days.

It was found that the best evidence that A.C.T.H. was being given in sufficient amount was a gain in weight, presumably from fluid retention. In addition, after a few days the patients usually felt better, their faces filled out, their appetites improved, and their temperatures fell. If the patient was too ill to be weighed, reliance had to be placed entirely on these general clinical observations. The eosinophil count was not found to be consistently helpful. The most suitable duration of treatment was also difficult of decision. Having worked up to a dose which appeared to be having effect, this was continued for two to five weeks. When the patient showed signs of improvement which appeared to be progressive the dose was gradually tapered off after a fortnight or so, another week or ten days being taken to stop it. In two cases the A.C.T.H. had to be temporarily stopped—because of excessive weight gain from fluid retention in one instance and because of hypokalaemia in the other. The gain in weight in 11 of the 12 patients who were fit to be weighed daily varied from 2 lb. to 1 st. 5 lb. (0.9 to 8.6 kg.), while one patient who showed an excellent clinical response did not gain weight while on A.C.T.H. These figures refer to gain in weight while actually on A.C.T.H.

## Results

The results are summarized in the Table. In all instances the treatment produced some effect, although this varied considerably in degree. Every patient experienced to some extent an improvement in appetite, a feeling of well-being, and a diminution in the fever. In some cases this did not happen until they had been on A.C.T.H. for as long as 14 days, but this was only in those cases which had been started on a smaller dose. Within two or three days of reaching an effective dose, or from starting treatment when the dose had been sufficient initially, these changes were noted, and indeed came to be used as an index that enough A.C.T.H. was being given. In some instances they were dramatic, and the temperature chart resembled a case of an infection treated with an antibiotic to which it was sensitive. In others it was much less striking, and on the whole it was most dramatic in those cases which afterwards did well. The subsequent course of the patients varied.

Six patients out of 14 made a complete recovery, which started coincidently with treatment with A.C.T.H. In all of these the mucosa has returned to normal or has the very finely granular but otherwise normal appearance usually seen in a case of ulcerative colitis which has recovered after having the disease for a long period. These six patients had been ill for periods varying from seven months to three years, with the exception of one who had been ill for only two months. One of them had been in hospital for eight months, receiving the usual treatment with transfusions, courses of antibiotics, etc., without improvement. One had been in hospital twice previously with slight or no improvement. In the remaining four it was their first admission to hospital. They were given routine treatment before A.C.T.H. was started, and had shown no improvement. These six cases have been followed up for periods varying from ten months to two and a half years, and only one of them has had a slight relapse, after six months, which cleared up in two to three weeks without hospitalization. This patient has since remained well for a further year. A seventh patient, who had almost recovered before her discharge, says she is now quite well, but declines to come back to hospital.

Improvement in bowel action in most cases began from five to fourteen days after the start of treatment, and usually about a week after the patient had begun to feel better. It became normal in two to three weeks in three cases, but in the remainder took from two to five months. Likewise, in these cases sigmoidoscopic improvement lagged far behind clinical improvement, and also behind symptomatic improvement in bowel action. The change from an acutely inflamed, hyperaemic bleeding mucosa with superficial ulceration to a reddened granular appearance was observed in two to three weeks, but the change from this latter to a normal or almost normal mucosa took from three to five months.

One case (No. 14) has been followed up for only five months; she showed considerable improvement in appetite and general condition, and some weight gain, but only a slight improvement in bowel action. It is not possible to generalize about the remaining six beyond that they all showed some improvement in appetite and had a feeling of well-being with some apparent improvement in general condition which began within a week in all cases, but usually within two or three days. Two patients (Cases 4 and 8) were men aged 35 and 25, who were not of the personality described as being typical of ulcerative colitis. They were in good jobs, which they were managing to do satisfactorily in spite of their disease. They both had slight obsessional trends, but were not obviously dependent personalities. Both these patients showed improvement, and both consider they have remained better after an interval of 21 months and 14 months respectively. Their stools are less frequent, although there is no definite change in the mucosa.

One case (No. 13), a man aged 27, was psychologically very immature, and his disease fluctuated strikingly with the amount of responsibility he had to undertake at his job. He was admitted in a fairly severe relapse, did very well with a course of treatment, and was discharged with only slight hyperaemia and granularity of his mucosa and symptomatically well. He relapsed after a few days at a convalescent home and was readmitted. A further course of treatment was again followed by recovery, and he was discharged, a suitable job having been found in advance. He has remained almost well since. This patient showed a childlike dependence on the ward staff, and his illness clearly had a considerable relation to his psychological state. It is, however, of interest to note that he spent 18 days in the secure atmosphere of the ward without improvement in his bowels on his first admission, while after a week on A.C.T.H. they were greatly improved. The same thing happened after four days on the second occasion. He gained 13 lb. (5.9 kg.) in weight during the first course of treatment and 7 lb. (3.2 kg.) during the second.

Case 9 was of particular interest. This patient, a woman aged 44 of childish mentality and below average intelligence, had been ill for a year with ulcerative colitis. After a course of A.C.T.H. she improved, and was discharged to a convalescent home with her bowel action almost normal, although the mucosa was still hyperaemic but greatly improved. She relapsed in a fortnight and was readmitted, her general condition having deteriorated considerably. She was given a prolonged course of A.C.T.H. This had to be interrupted because of oedema, and hypokalaemia without symptoms, on two occasions, but she gained 1 st. 5 lb. (8.6 kg.) in two months. There was slight weight loss on first stopping the A.C.T.H., but she then continued to gain weight, putting on a further 7 lb. (3.2 kg.) in the next month. Her general condition was vastly improved, but she continued to have profuse diarrhoea and the mucous membrane remained abnormal. An ileostomy and a colectomy were finally performed, and the patient was discharged cured of her ulcerative colitis, but with intermittent bleeding from the rectal stump. Although this patient had been acutely ill with diarrhoea, at one stage having meteorism and requiring intravenous fluids on and off for about a fortnight, her colon showed no ulceration at operation and the pathologist reported minimal inflammatory changes with general thinning of the mucosa throughout the whole colon. It subsequently transpired that this mentally unstable woman had been aggravating her illness by taking Epsom salts, but when and how much was never discovered.

Of the two remaining cases, one was a woman of 62 (Case 3) who came in with a fulminating relapse. She went downhill rapidly on routine treatment, and after 14 days

was started on A.C.T.H. There was temporary improvement for a period of two to three weeks. The stools decreased from 25 to 10 a day and became more formed. She subsequently developed a monilia infection, pyoderma gangraenosum, and bronchopneumonia, which proved fatal. The other case was that of a man of 28 (Case 5) who had been ill for a year. The condition had become fulminating, and he had shown no definite improvement with antibiotics, transfusions, and other routine treatment over a period of two months. A course of A.C.T.H. did produce a temporary improvement, and an ileostomy was done. After a stormy course the patient got over this, but further colonic bleeding and fever necessitated colectomy, following which the patient died. In both these fulminating cases A.C.T.H. produced a temporary improvement. They were both treated early in the series, and with more experience would have been given A.C.T.H. earlier.

## Discussion

Experience in this small series has been similar to the reported findings in American papers. The remarkable subjective improvement, feeling of well-being, increase in appetite, and fall in fever, together with an improvement in the general condition of the patient, have been noted to precede any change in the bowel function or bowel mucosa by an appreciable interval, when this occurs. All seven patients who recovered might have recovered spontaneously. The striking fact about these cases was not that they recovered, but that this recovery started coincidently, and often dramatically, with the giving of A.C.T.H., although in many instances it took as long to complete as might have been expected in a spontaneously recovering case. The sequence of events in the cases which recovered would suggest that A.C.T.H. exerts an effect on the patient's general condition which is followed later by recovery of the bowel disorder, rather than having a specific effect on the colon itself. Indeed, this general effect was observed in all cases in some degree, whether or not it was followed by recovery of the colonic mucosa.

It is felt that any effect this treatment may have is entirely non-specific so far as the ulcerative colitis is concerned, but it appears to have some general stimulating effect on the patient, which at times may be sufficient to initiate the process of recovery. It has been argued that A.C.T.H. produces benefits in this condition entirely by its euphoriant effect, which is subsequently reflected in the improvement in the disease. It may well be that the production of euphoria is an important factor in the action of A.C.T.H., but in some cases the physical changes, such as fall in temperature, are so dramatic in their onset and occur coincidently with, if not before, the change in mental outlook, that it would be difficult to argue that they resulted therefrom. A simpler and more probable explanation would be that both resulted from a physical effect of the A.C.T.H., however much the euphoria may later contribute to the patient's recovery by assisting him to face up to and adjust to his difficulties. While none would deny the great importance of psychological factors in ulcerative colitis, it must be remembered that chronic abdominal disorders, as, for example, amoebic dysentery, are notoriously associated with changes in the mental state, which returns to normal with recovery of the disease.

None of the cases which recovered had evidence of fibrosis and stricture formation. They all had severe acute inflammatory changes in the mucosa, with ulceration at some stage, but the longest history was three years, in Case 2, and she had had a partial remission for one year of this period. The changes in the case said to have recovered (Case 1) were also of that type, although she had a nine-years' history, but it appeared that she had only had a proctitis for the first three or four years of this time. These seven patients were all women aged between 20 and 36. Three were married and four were single. Of the three who were married two had children. It is perhaps noteworthy that these were the only women in the series between those ages. It is not known that ulcerative colitis in women of this age group has a better prognosis than in other age groups.

It would seem that the treatment is quite safe provided the usual precautions are observed and the possible complications are kept in mind. In this series hypokalaemia has been observed twice, once with symptoms, and necessitated temporary cessation of treatment. On one occasion gross fluid retention called for stoppage of the drug for a few days. A previous history of peptic ulcer has resulted in patients being excluded from treatment with A.C.T.H., and the presence of very severe tenderness, or guarding, over the colon, suggesting acute involvement of the serosa with the possibility of incipient perforation, has also made us refrain from using A.C.T.H. on occasions. The presence of other infection, particularly tuberculosis, might contraindicate its use. A serious complication has been seen by one of us (A. G. B.) in a case, not in this series, under the care of Dr. Una Ledingham, who has kindly given permission for it to be quoted. A man aged 48, who had had acute ulcerative colitis for six weeks, collapsed on the second day of treatment with A.C.T.H., and became unconscious with profound hypotension and an electrolyte disturbance very suggestive of acute adrenal insufficiency. He responded to treatment with "eucortone" and intravenous salines, and subsequently recovered after an ileostomy performed while on cortisone. This case is similar to the one reported by Wilson and Roth (1953), but their patient, who had ulcerative colitis, developed symptoms just after the cessation of treatment and died. Necropsy showed massive adrenal haemorrhages.

It would appear at the present time that A.C.T.H. has a definite place in the management of this disease. It is not regarded as desirable to use it in very mild cases. It would seem to be most helpful in acute cases of fairly recent onset with severe inflammatory changes in the mucosa, and, in the opinion of some workers, particularly in those in whom there is a severe constitutional disturbance. It clearly offers much less hope of any permanent benefit in long-standing chronic cases with fibrotic changes in the colon, although it may help to tide the patient over an acute exacerbation of the condition. It seems that in some recent cases it may help to initiate the process of recovery, which may become complete. In others it may be of use in improving the patient's condition sufficiently to allow of elective surgery. In a severe fulminating case the possibility of benefit from this treatment should not allow surgery to be delayed unduly, although recovery from ulcerative colitis is sometimes so unexpected and complete that the irreversible procedure of ileostomy and colectomy should be postponed until it is clear that further delay might render it unsafe.

## Summary

Fourteen cases of ulcerative colitis have been treated with A.C.T.H.

In seven cases the start of a complete remission coincided with the administration of A.C.T.H. In four cases a varying degree of maintained improvement occurred. Transient improvement of slight degree was noted in three cases.

Experience in the treatment of ulcerative colitis with A.C.T.H. is discussed, and it is concluded that A.C.T.H. has a place in the management of certain cases of the disease, particularly acute and severe cases of fairly recent onset.

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# ARE DIABETIC DEGENERATIVE COMPLICATIONS PREVENTABLE?*

BY

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There are few diseases about which we are so knowledgeable and yet so ignorant as diabetes mellitus. We realize how the metabolic disturbance conflicts with physiological integrity, and how by taking even a little thought and modest action the diabetic can avoid the immediate lethal effects of the disease, which were so formidable in the pre-insulin era, and can live a life, for a considerable time at any rate, which is not far short in well-being from that enjoyed by normal people. Nevertheless the diabetic state itself is so far incurable, and we are largely ignorant not only of its aetiology but also of the cause of most of its complications.

When I was a student and young doctor we were entirely occupied, so far as diabetes was concerned, with endeavouring to keep the patient alive for a while, and, apart from gangrene, we were taught little of its ultimate complications, for relatively few patients had by then lived long enough to develop them. To-day the problem is not so much that of the acute disease as exemplified by diabetic coma, for we know or ought to know how to avoid that disaster, as it is of a chronic disorder with a considerable expectation of life which involves a prolonged effort to avoid the degenerative complications which so commonly ensue. These are most distressing when they occur in relatively young patients in the third or fourth decade—when, if they were not diabetic, they might expect to be in the prime of life—and are particularly tragic when they involve blindness. Are these complications to be regarded fatalistically as being due to something inherent in the diabetic process, like the large babies of diabetic and pre-diabetic mothers—the inevitable sequel in a shorter or longer time, of the diabetic state? Or can they be prevented by care and trouble directed to the control of the metabolic disturbance?

## Two Points of View

In my younger days I had no doubts on this point. If you were a good diabetic and kept the commandments you not only remained well so far as good nutrition and the avoidance of ketosis were concerned but you avoided the later complications of the disorder; whereas if you were bad you reaped the harvest of tares. I think it was the study of diabetic pregnancy and the high foetal loss rate which occurred in the pre-diabetic obstetrical history of the mothers which introduced doubt into my simple faith and ushered in a period of agnosticism, during which time I flirted with the use of the so-called "free diets" in treatment. In this system hyperglycaemia and glycosuria were largely disregarded and the criteria adopted to govern insulin dosage were freedom from hunger, thirst, nocturia, and ketosis, and the maintenance of weight and energy on the one hand; and the avoidance of hypoglycaemia on the other. It did not matter very much how great the quantity of sugar lost in the urine so long as enough insulin was administered to ensure an efficient carbohydrate utilization from the abundant intake.

The advocates of this system—and there were and still are many—claim that patients benefit psychologically from this form of treatment through freedom from irksome restrictions imposed upon their daily life; that "each meal which should be an elegant satisfaction of appetite is not turned into a problem in arithmetic and a trial of self-abnegation"; that patients are better nourished and therefore more resistant to infections, including tuberculosis; that in children growth and sexual development are satisfactory; and that in women the incidence of pregnancy is high. Lichtenstein (1945), who followed up a group of patients so treated for ten years, claimed that the incidence of degenerative complications in them was not unduly high. Dolger (1947), who observed 200 diabetics over a period of 20 years, found that vascular disease occurred neither sooner nor more frequently in those with persistent glycosuria than in those kept relatively sugar-free. A similar conclusion was reached by Goodof (1945) in relation to the nephropathy of diabetes. As for diabetic retinopathy, Ballantyne (1946) stated: "The outstanding paradox is the lack of any apparent relation between the severity of diabetes, the control of the condition by treatment, and the presence or absence of retinal changes." Goadby (1950) and Hunt (1951) are both sceptical of the value of careful dietetics in the prevention of the vascular complications. Finally, there is Mirsky's (1946) profoundly pessimistic profession of therapeutic nihilism, which also contains a statement of the obvious: "It makes little difference how the diabetic is treated; if he lives long enough, he will develop one or another form of vascular disease."

Opposed to this point of view are those who believe that every effort should be made to restore physiological conditions, including freedom from glycosuria and a normal blood-sugar concentration so far as this is possible. Joslin, with his vast experience of diabetes, has thundered against the *laisser faire* heresy in its treatment with a puritanical evangelistic fervour. Good diabetic control, he maintains, can be reached only along the thorny path of scrupulous dietetics, and the sin of diabetics who reject this commandment is sure to find them out in a shorter or longer time (Joslin *et al.*, 1952). During the last five years several surveys have been made by other workers (Whittaker, 1949; Jackson *et al.*, 1950; Root *et al.*, 1950; Wilson *et al.*, 1951a, 1951b, 1951c; Spoont *et al.*, 1951; Beaser, 1951; Hall, 1952; Keiding *et al.*, 1952) which have suggested that there is an undoubted correlation between the control of the disease and the incidence of its complications.

## The "Free Diet"

Some years ago we (Forsyth, Kinnear, and Dunlop, 1951) published the result of our observations on 50 diabetics treated with a "free diet" for five years. During that time seven patients—all of them young—showed a progressive worsening of their diabetic state and had to revert to controlled diets. The change was also necessary for two patients who suffered from frequent insulin reactions, and for two others who became obese and developed pruritus. The results, however, were satisfactory in the remaining 39 patients in whom episodes of ketosis or hypoglycaemia were not more numerous than in other patients treated on more conventional lines, and their general health and happiness seemed in some respects to be superior. It was fortunate that we stressed the fact that five years was much too short a time on which to base conclusions regarding the

*Extract from the Lumleian Lectures on the "Complications of Diabetes" delivered at the Royal College of Physicians on April 6 and 8, 1954.

TABLE I.—50 *Diabetics Treated with a "Free" Diet*

| | | |
|---|---|---|
| 1945–50: | | |
| Progressive deterioration in sugar tolerance | 7 | 11 |
| Frequent severe hypoglycaemia | 2 | |
| Obesity and pruritus | 2 | |
| 1950–4: | | |
| Obesity and pruritus | 3 | 30 |
| Tuberculosis (all forms) | 9 | |
| Retinopathy, neuropathy, etc. | 14 | |
| Cardiovascular deaths | 4 | |
| Satisfactory | 9 | |

desirability of the regime. For, as can be seen from Table I, the results in this group of patients during the succeeding four years have been disastrous, particularly as regards the incidence of tuberculosis. Only 9 of the original 50 patients are still in good shape at the end of nine years. The series is small but nevertheless suggestive. No random selection of groups of 50 diabetics on controlled diets has shown such unfavourable results over the same period.

### Diabetic Control in Presence of Complications

In preparation for this lecture I have, during the last few months, personally examined 167 patients who have attended our dietetic department for periods of time varying from 15 to 31 years, and have attempted to correlate the degree of control of their diabetes with the incidence of tuberculosis, neuropathy, and degenerative complications. None of the patients were very mild diabetics in that they had all required at least 20 units of insulin a day during the many years of their attendance, but they were otherwise unselected. I awarded marks to each patient according to the number and severity of the five main complications present—tuberculosis, retinopathy, cardiovascular disease, nephropathy, and neuropathy—three marks being given for severe, two for moderate, and one for slight involvement in each case. Thus a severely tuberculous, blind, hypertensive, gangrenous diabetic with advanced nephropathy and neuropathy would score the possible—15; while a patient with no complications at all, to whom Joslin would give a gold medal, would score 0.

From the records which we keep in our department I attempted to separate the degree of diabetic control achieved in each case into three main classes—good, fair, and poor. This was not easy to do. The treatment of most diabetics viewed in retrospect constitutes a record of success and failure, of discipline and licence. The requirements I adopted before classifying a patient in the good class, were, however, very stringent. Any long period of significant glycosuria or even a short one of severe ketosis disqualified the patient from that class. The out-patient case sheets of the patients accepted for the good class thus disclosed year after year a record of sugar-free tests when they reported, or only occasional and moderate glycosuria. It has to be realized, however, that the diabetic condition of no patient requiring a significant amount of insulin is perfectly controlled over 15 to 31 years' time, in the sense that the urine is *always* sugar-free and the blood *always* normoglycaemic. One deals perforce with individuals whose diabetes has been under varying degrees of inadequate control and one speaks of the best of them as having good control. Nevertheless, I think rough justice was done in the classification.

Table II shows the results. Of the 167 patients, 75 (45%) had to be classified as having been under poor control because during their 15 to 31 years of diabetes hyperglycaemia and glycosuria had been very common and incidents of ketosis not infrequent; 53 (32%) had been much better controlled though their records were by no means unblemished; and there were 39 patients who were accepted for the class of good control according to the rather stringent qualifications already outlined. The patients in the three classes were not dissimilar in the number of old or young in each, and they were all, as has been said, taking over 20 units of insulin a day. It will be seen, however, that the marks allotted to them for complications were strikingly different—the complication index in the poor control group being three times that in the good-control group.

TABLE II

| Control | No. of Patients | Total Score | Average per Patient |
|---|---|---|---|
| Good | 39 (23%) | 66 | 1·7 |
| Fair | 53 (32%) | 149 | 2·8 |
| Poor | 75 (45%) | 382 | 5·1 |

Of the 167 patients, only 27 (16%) seemed to be entirely free from complications and achieved in consequence 0 marks. Again it will be seen (Table III) that such patients were four to five times more common in the good than in the poor group.

TABLE III.—*Incidence of Complications*

| | Good | Fair | Poor | Total |
|---|---|---|---|---|
| No. of patients | 39 (23%) | 53 (32%) | 75 (45%) | 167 (100%) |
| No. without complications | 13 (33%) | 9 (17%) | 5 (7%) | 27 (16%) |
| No. with retinopathy | 17 (44%) **1·8** | 25 (47%) **1·7** | 59 (79%) **2·0** | 101 (60%) |
| No. with C.V.S. complications | 18 (46%) **1·2** | 33 (62%) **1·5** | 54 (72%) **1·6** | 105 (63%) |
| No. with nephropathy | 2 (5%) **2·0** | 4 (8%) **2·0** | 26 (35%) **2·1** | 32 (19%) |
| No. with tuberculosis | 2 (5%) **1·5** | 3 (6%) **1·7** | 6 (8%) **2·2** | 11 (6%) |
| No. with neuropathy | 9 (23%) **1·0** | 28 (53%) **1·5** | 61 (81%) **1·7** | 98 (59%) |

**Bold figures give the average severity index: maximum 3.**

When the incidence and the severity of individual complications are examined similar trends are obvious and invariable. Out of the 167 patients, 101 (60%) had ophthalmic complications. These were more numerous and severe in the poorly controlled group in comparison with those well controlled—those with fair control occupying an intermediate position (Table III).

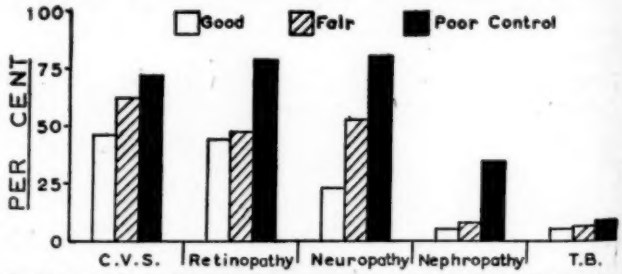
Cardiovascular complications, as evidenced by hypertension, coronary disease, defective pulsation in the dorsalis pedis and posterior tibial arteries, calcification of arteries, or gangrene, were present in 63% of the patients—the incidence and severity showing the same trends as before in the three groups (Table III).

Nephropathy was present in 19% of the patients, being very much more common in the poorly controlled group (Table III).

Six per cent. of the patients were tuberculous. Though the trend is the same, the figures are too small to be significant (Table III).

Neuropathy was present in 98 (59%) of the patients, and of all the complications its incidence and severity presented the most striking correlation with the degree of control achieved (Table III). Diabetic retinopathy, nephropathy, and neuropathy are all, in some as yet ill-understood way, the result of the metabolic disorder, but whereas the incidence of the two former is considerably affected by the duration of the diabetes the incidence of neuropathy is determined almost entirely by neglect of diabetic control.

These figures, which are summarized in the Chart, are not unlike those obtained from similar recent surveys by other workers, and particularly the extensive studies of Wilson *et al.* (1951a, 1951b, 1951c). As the result of this and my experience of "free diets" I have returned to my original simple diabetic faith. I believe that whatever specific aetiological factors may be causing diabetic degenerative lesions—endocrine, infective, or metabolic—the careful control and




Incidence of complications: percentage of patients affected in each group.

aggressive treatment of the disorder over the years is a most important factor in their prevention or postponement. I believe that to obtain good control diabetic diets should not usually contain much more than 200 g. of carbohydrate; that patients should be initially trained in the hard school of food-weighing, for it is only in that way that they learn to appreciate quantities; and that they should report regularly to a diabetic clinic to be assessed as regards symptoms, weight, glycosuria, and occasionally blood-sugar concentration, and, depending on the findings, to have their insulin dosage and diet suitably altered, for it is most exceptional to encounter a well-controlled diabetic who has been made entirely responsible for his own treatment.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# SULPHONAMIDE PROPHYLAXIS IN CHRONIC BRONCHITIS

## A CLINICAL TRIAL


BY

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A clinical trial was carried out to determine whether the continuous administration of small doses of one of the sulphonamide drugs through the winter months would reduce the frequency and severity of the attacks of "winter bronchitis" which are common in cases of pneumoconiosis, emphysema, and "chronic bronchitis." The seriousness of the problem in general practice has been emphasized by Pemberton (1949) and Fry (1953, 1954), while Goodman *et al.* (1953) have stressed its importance as a cause of morbidity and mortality in the country. Energetic treatment by means of penicillin and streptomycin (Mulder *et al.*, 1952) is usually effective in an established attack, but if prophylaxis were possible much disability might be prevented and economy of hospital facilities achieved.

### Plan of Investigation

Strict criteria for the suitability of a subject for inclusion in the trial were laid down initially. Subjects were included only if they gave a clear-cut history of having had an attack of increased cough and purulent sputum, necessitating their going to bed or being off work for more than one day, in each of the two previous winters. Those with conditions such as rheumatic or hypertensive heart disease, cor pulmonale, rheumatoid arthritis, or pulmonary tuberculosis, which might lead to periods of illness unassociated with bronchitis, were excluded. A medical and industrial history was taken from each subject, followed by a clinical examination and a chest radiograph. The appearance of the sputum was noted, but no bacteriological examinations were made.

*Methods of Assessment.*—Previous experience suggested that all attacks of "bronchitis" were not similar and that a satisfactory classification and method of assessment would not be easy. This difficulty has been noted by Lister (1949), Oswald *et al.* (1953), and Fry (1954). We paid particular attention to the subject's history of the types of attack experienced, which were classified as follows:

*Type A1.*—A typical unmodified attack of winter bronchitis as severe as any previous one, with increased cough and purulent sputum causing the subject to stay off work and usually retire to bed.

*Type A2.*—A less severe variant of A1, the subject not having to stay off work, there being less cough, and the sputum being less in both amount and purulence.

*Type B.*—An attack of tightness of the chest or bronchial spasm without any change in cough or sputum.

*Type C.*—A typical "head cold" or influenza without involvement of the lower respiratory tract.

It was decided that the attacks should be assessed by one person, and, although some difficulty in classification was occasionally encountered, on the whole the system worked well.

The investigation took place in two stages, while the subjects fell into three separate groups.

### Stage I

*Group 1.*—In the winter of 1951–2 35 subjects were selected from men with pneumoconiosis (simple or complicated) who had attended the Pneumoconiosis Research Unit and from men with emphysema and "chronic bronchitis" who were under the care of general practitioners near Llandough Hospital. It had been hoped that a much larger number of suitable subjects would be found: the trial was begun in November, and extra subjects were included, as they became available, until the beginning of January, when it was decided that further additions should cease. As they were selected, subjects were allocated to either a "treated" or a "control" group on a random basis in such a way that neither they nor the medical assessor knew to which group they had been assigned.

The treated group were given one tablet of sulphadimidine (0.5 g.) three times a day (on waking, at mid-day, and before retiring), and the control group an indistinguishable but inert tablet at the same times. The purpose of the trial was explained to each subject's own doctor in a letter, and each subject was issued with one week's supply of tablets at a time, with written instructions on when to take them; it was explained that they must report any sore throat or skin rash. The majority of subjects started taking the tablets in November, and the remainder had begun by the beginning of January; all stopped at the end of April. Information on the date and duration of any illness or absence from work was obtained weekly, and a clinical examination was carried out monthly. Frequent interviewing is considered very important, as people with chronic cough and sputum often have difficulty in establishing the precise date of onset of an attack of bronchitis.

When the results of this first small experiment had been evaluated it was found that differences suggestive of a benecial effect of the drug had occurred. It was therefore decided to start a subsequent trial rather earlier in the autumn and increase the number of subjects. Accordingly, Stage II of the trial was planned for the winter of 1952–3, this time using two groups of subjects chosen in exactly the same way.

### Stage II

*Group 2.*—This group comprised 30 men from a factory in a South Wales valley employing a large proportion of ex-coal-miners with pneumoconiosis.

*Group 3.*—This group comprised 32 subjects (27 men and 5 women) from an out-patient clinic in Stoke-on-Trent. A few had "chronic bronchitis," but the majority were ex-pottery-workers with pneumoconiosis.

Again much smaller numbers of suitable subjects had been found than was hoped for, but, provided that differences of a magnitude similar to or greater than those in Stage I occurred again between treated and control groups, the numbers were sufficient to establish significance. Accordingly the second stage was continued, methods of administration of the tablets and assessment of attacks being the same as in Stage I.

### Results of Trial (Both Stages)

In group 1, eight patients stopped taking the tablets, two of them had definite sulphonamide sensitivity in the form of a skin rash. In group 2 there were four lapses, and in group 3 two lapses. The various reasons for ceasing to take the tablets are given in Table I.

The age distribution of the various groups of subjects remaining in the trial is given in Table II. It will be seen that the groups were all very similar in age, and that the random allocation into treated and control subjects was fairly successful in making the groups comparable, although the treated group contained rather more older subjects.

TABLE I.—*Lapses—All Groups*

| Reason for Stopping Tablets | Treated Group. No. of Patients | Control Group. No. of Patients |
|---|---|---|
| Skin rash—i.e., definite sulphonamide sensitivity | 2 | 0 |
| Non-attendance | 0 | 2 |
| Giddiness | 1 | 0 |
| Headache, nausea, and vomiting | 1 | 0 |
| Worsening of respiratory symptoms | 3 | 4 |
| Died of other causes | 1 | 0 |
| Total | 8 | 6 |

TABLE II.—*Age Distribution of Subjects in Trial*

| | | Date of Birth | | | | | All Ages |
|---|---|---|---|---|---|---|---|
| | | 1870– | 1880– | 1890– | 1900– | 1910–20 | |
| Group 1 | Control | — | 2 | 8 | 3 | 1 | 14 |
| | Treated | — | 3 | 5 | 5 | — | 13 |
| | Total | — | 5 | 13 | 8 | 1 | 27 |
| Group 2 | Control | — | — | 5 | 7 | — | 12 |
| | Treated | — | 1 | 4 | 8 | 1 | 14 |
| | Total | — | 1 | 9 | 15 | 1 | 26 |
| Group 3 | Control | — | 5 | 9 | 1 | — | 15 |
| | Treated | 1 | 6 | 6 | 2 | — | 15 |
| | Total | 1 | 11 | 15 | 3 | — | 30 |
| All groups | Control | — | 7 | 22 | 11 | 1 | 41 |
| | Treated | 1 | 10 | 15 | 15 | 1 | 42 |
| | Total | 1 | 17 | 37 | 26 | 2 | 83 |

TABLE III.—*Distribution of Subjects with A1 Attacks*

| | | No. of Subjects | | Total |
|---|---|---|---|---|
| | | Attacked | Not Attacked | |
| Group 1 | Control | 7 | 7 | 14 |
| | Treated | 2 | 11 | 13 |
| | Total | 9 | 18 | 27 |
| Group 2 | Control | 4 | 8 | 12 |
| | Treated | 4 | 10 | 14 |
| | Total | 8 | 18 | 26 |
| Group 3 | Control | 3 | 12 | 15 |
| | Treated | 6 | 9 | 15 |
| | Total | 9 | 21 | 30 |
| All groups | Control | 14 | 27 | 41 |
| | Treated | 12 | 30 | 42 |
| | Total | 26 | 57 | 83 |

The analysis was confined to attacks classified as A1 or A2. Table III shows the distribution of subjects who had A1 attacks, in the three groups separately and in combination. Only in group 1, as has been mentioned above, was there any suggestion that the treated subjects did better than the controls ($0.10>P>0.05$). The proportions attacked in the combined data (34% of controls, 29% of treated) did not differ significantly ($0.8>P>0.7$), and a $\chi^2$ test, applied to see if the three groups differed significantly between themselves in the proportions of treated and controls attacked, also gave a negative answer ($0.10>P>0.05$). When A1 and A2 attacks are considered together, all suggestion of an effect of treatment is lacking. Table IV shows the distribution of subjects who had A1 or A2 attacks. Significance tests are clearly not required.

TABLE IV.—*Distribution of Subjects Having A1 or A2 Attacks*

| | | No. of Subjects | | Total |
|---|---|---|---|---|
| | | Attacked | Not Attacked | |
| Group 1 | Control | 9 | 5 | 14 |
| | Treated | 8 | 5 | 13 |
| | Total | 17 | 10 | 27 |
| Group 2 | Control | 9 | 3 | 12 |
| | Treated | 8 | 6 | 14 |
| | Total | 17 | 9 | 26 |
| Group 3 | Control | 6 | 9 | 15 |
| | Treated | 9 | 6 | 15 |
| | Total | 15 | 15 | 30 |
| All groups | Control | 24 | 17 | 41 |
| | Treated | 25 | 17 | 42 |
| | Total | 49 | 34 | 83 |

So far only the numbers of subjects attacked have been compared. It is possible, however, that treatment might reduce the frequency of attacks in the same subject. Only three subjects had as many as two A1 attacks—two of these being in the group 1 control group, one in the group 2 treated group. In consequence, in group 1 the average number of A1 attacks per man differs almost significantly ($0.10>P>0.05$) between the treated (0.15 attacks per man) and control groups (0.64 attacks per man). When all the groups are combined the overall difference is not remarkable. Table V shows the distribution of attacks per subject. There were 29 attacks in all, 16 among the controls, 13 among the treated. Twenty-three subjects had one attack each (12 controls and 11 treated), and, as has been said, two controls and one treated subject had two attacks each. The average number of attacks per man was 0.39 for the controls, 0.31 for the treated, and this difference is not statistically significant ($0.5>P>0.4$). When A2 attacks are included the distributions are even more alike (Table VI). Three subjects in each group had three attacks; six controls and four treated had two attacks; 15 controls and 18 treated had one attack. The average number of attacks per subject was 0.88 for the controls, 0.83 for the treated.

TABLE V.—*Distribution of A1 Attacks*

| No. of Attacks | No. of Subjects | | Total |
|---|---|---|---|
| | Controls | Treated | |
| 0 | 27 | 30 | 57 |
| 1 | 12 | 11 | 23 |
| 2 | 2 | 1 | 3 |
| Total | 16 | 13 | 29 |
| Average no. per man | 0·39 | 0·31 | 0·35 |

It might be thought that the subjects were insufficiently alike in their tendency to have attacks for these averages to have much meaning. The results do not confirm this criticism, however. If the risk is the same for each subject, the numbers having no attacks, one attack, two attacks,

etc., should be predictable from the terms of a Poisson series. Table VI shows the expected numbers if each man has in fact an equal risk of attack. Clearly, the agreement is quite close, and there is little suggestion that unusually resistant or susceptible subjects were included in the trial.

TABLE VI.—*Distribution of A1 or A2 Attacks*

| No. of Attacks | Controls | Treated | Total | Expected |
|---|---|---|---|---|
| 0 | 17 | 17 | 34 | 35·0 |
| 1 | 15 | 18 | 33 | 30·2 |
| 2 | 6 | 4 | 10 | 12·9 |
| 3 | 3 | 3 | 6 | 3·7 |
| 4 or more | — | — | — | 1·0 |
| Total .. | 36 | 35 | 71 | 71·1 |
| Average no. per man | 0·88 | 0·83 | 0·86 | 0·86 |

The number of subjects fulfilling the criteria laid down for inclusion in the trial was much smaller than expected. In consequence the trial was an insensitive one, and quite large real effects for sulphonamide are compatible with the negative results obtained. For example, the proportion of all subjects having an A1 attack was 31.3% (26 out of 83). Attacks occurred in 28.6% of the treated subjects and in 34.1% of the controls, a difference of 5.5% in favour of sulphonamide. If the overall attack rate is taken as fixed, the observed results for the treated group are not less probable than 0.05 if their true attack rate was as little as 19% or as much as 40.5%. That is to say, any true attack rates giving sets of results lying between the two extremes shown in Table VII cannot be ruled out on present evidence. More generally, without fixing the overall attack rate, various combinations of attack rates in the separate groups can be shown to be possible without conflicting with the present results,

TABLE VII.—*Extreme Results Compatible with Observed Figures*

| | | A1 Attacks | None | Total |
|---|---|---|---|---|
| Favourable to treatment | Controls .. | 18 (43·9%) | 23 | 41 |
| | Treated .. | 8 (19·0%) | 34 | 42 |
| | Total .. | 26 (31·3%) | 57 | 83 |
| Unfavourable to treatment | Controls .. | 9 (22·0%) | 32 | 41 |
| | Treated .. | 17 (40·5%) | 25 | 42 |
| | Total .. | 26 (31·3%) | 57 | 83 |

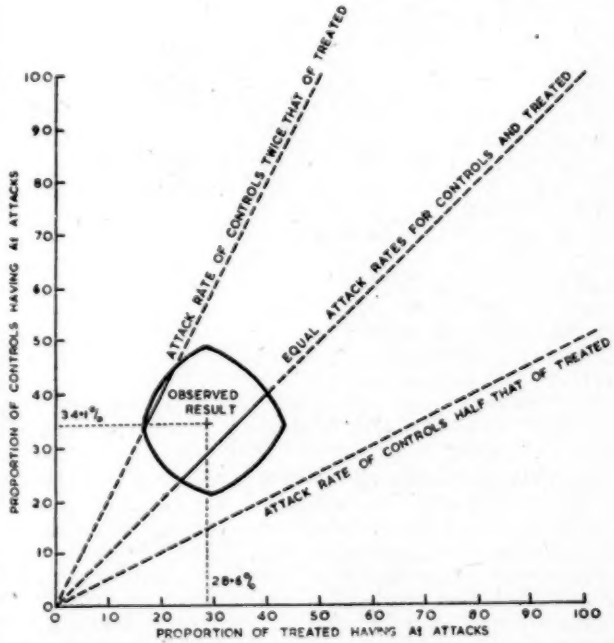


Chart showing range of effects of sulphonamide. The closed curve shows the zone within which any combination of attack rates is not too improbable ($P>0.05$) in view of the observed result.

provided that the resultant point on the graph lies within the closed curve shown in the Chart. For example, equal attack rates ranging from 24 to 40% are possible; if the rates for the control group lie between 34 and 45% the rates for the treated group can be half as great, while it is in no wise possible for the treated group attack rates to be twice as great as the control group rates. The Chart illustrates the very large range of different effects of sulphonamide which are compatible with the observed results, or, in other words, the great insensitivity of a small trial of this kind.

## Discussion

The continuous administration of small doses of one of the sulphonamide drugs has been employed in the prophylaxis of rheumatic fever and meningococcal infections. One of these drugs (usually sulphadiazine) has been used as a prophylactic against respiratory infections, and favourable results were reported by Watson *et al.* (1943), Hodges (1944), Coburn (1944, 1945), and Billow and Albin (1946). These authors give accounts of controlled trials in the American Services during the 1939–45 war, but it should be remembered that the subjects were practically all young healthy recruits, and that the organism responsible for the acute respiratory illnesses was usually the streptococcus. Subsequently doubt was cast upon the advisability of "mass chemoprophylaxis," as increasing numbers of sulphonamide-resistant streptococci were found in cases both in the Services and in the general population (Epidemiology Unit Number 22, 1945; Delamater *et al.*, 1946; Wilson, 1946; Roberg, 1946; Damrosch, 1946; Johnson and Hartman, 1947). These authors thought that sulphonamide prophylaxis was ineffective and possibly dangerous. Kuh and Collen (1949) found that penicillin was ineffective prophylactically, but Gezon *et al.* (1953) carried out an investigation comparing oral penicillin, sulphonamides in small doses, and aspirin for the prophylaxis of respiratory infections, and reported favourable results in the penicillin and sulphonamide groups. The latter authors stressed the difficulty of diagnosis of acute respiratory infections and found that streptococci were responsible for only a third of their cases, the remainder being caused by other bacteria and viruses. In this country, Joules (1953) has advocated the use of 1 g. of sulphonamide daily in chronic bronchitis.

Many investigations of the bacteriology of the sputum in bronchitis have been made, but it is difficult as yet to assess the significance of the findings. It appears that pneumococci and *Haemophilus influenzae* (Stuart-Harris *et al.*, 1953; May, 1953a) are frequently present, and that other organisms such as *Streptococcus viridans* and *Neisseria catarrhalis* are probably non-pathogenic. The precise role of viruses has yet to be established, but it is suggested by Stuart-Harris *et al.* (1953) that they may play a part in the acute exacerbations.

According to May (1953a) there is a significant association between purulent sputum and the presence of potential pathogens, especially pneumococci and *H. influenzae*. He also found that suitable chemotherapy could render purulent sputum mucoid in character, but that a return of purulent sputum was common on cessation of therapy. Furthermore, it was found that patients expectorating mucoid sputum only did not benefit from chemotherapy, and, in some, the change from purulent to mucoid sputum resulted in an increased viscidity of the sputum with consequent difficulty in expectoration (May, 1953b). Elmes *et al.* (1953) investigated the effect of various antibiotics on the sputum in chronic bronchitis, and came to the conclusion that none of the drugs at present available was suitable for the prophylaxis of acute exacerbations.

So far as our trial is concerned there are several possible reasons why sulphonamide was not found to be effective as a prophylactic agent. Its true effect may lie within the zone of uncertainty in the Chart, so that it is too small to be established by a trial of this size. The classification of the attacks may have been erroneous, or the subjects not really true "chronic bronchitics." The majority of subjects in this

trial had industrial lung disease, and it is possible that such subjects may be less likely to respond to prophylactic chemotherapy than those who have not been exposed to a dust hazard. One of the sulphonamide series may not, in fact, have been the best drug to choose: the administration of drugs (such as penicillin) by injection was thought to be impracticable with working subjects, while the possible undesirable side-effects of chloramphenicol (Franklin and Garrod, 1953) and aureomycin—apart from the expense of these two drugs—would hardly justify their use over prolonged periods for prophylaxis, although good results have been claimed recently for the continuous administration of aureomycin in preventing acute respiratory infections in patients with congestive cardiac failure (McVay *et al.*, 1953). The dosage of sulphonamide may have been inadequate to establish a sufficiently high blood level, and the production of sulphonamide-resistant organisms may have been stimulated, but larger doses would probably have produced toxic effects.

In conclusion it may be said that at present there is no evidence that a suitable drug for the prophylaxis of the acute exacerbations of chronic bronchitis exists, but that if and when such evidence became available, as a result of a controlled trial, much disability might be prevented. In seeking such a drug much help would be obtained if more were known about the epidemiology, clinical types, bacteriology, and pathology of chronic bronchitis.


### Summary

The acute exacerbations of "winter bronchitis" that occur in pneumoconiosis, emphysema, and "chronic bronchitis" are a serious problem.

A controlled clinical trial is described in which subjects with various forms of chronic bronchitis were studied in three centres during the winters of 1951–2 and 1952–3. In all, 83 subjects were included. Of these, 42 were given 0.5 g. of sulphadimidine three times a day during the winter months and 41 were given inert tablets in the same way.

A clinical assessment of the subjects was made at monthly intervals. Acute exacerbations of respiratory symptoms were classified as follows: (1) an acute "unmodified" attack of bronchitis; (2) a modified and less severe attack of bronchitis; (3) an attack of bronchial spasm; and (4) a head cold or "influenza."

No evidence was found that sulphonamide was effective in preventing the acute exacerbations of "winter bronchitis," but the trial was relatively insensitive.


We acknowledge our indebtedness to Dr. C. M. Fletcher (previously director of this unit), at whose instigation the trial was planned; to Dr. J. C. Gilson (director) for his advice and criticism; to our colleagues in the unit, especially Dr. I. Davies and Dr. M. C. S. Kennedy (M.R.C. Silicosis Treatment Centre, Stoke-on-Trent), who helped in the running of the trial; also to the general practitioners who referred patients. We are grateful to the Imperial Chemical (Pharmaceuticals) Ltd. for the supply of the tablets used, and to the Austin Motor-Car Company for facilities afforded.


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# ACUTE APPENDICITIS IN CHILDHOOD


BY

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A review of a personal series of 118 cases of acute appendicitis treated in conjunction with the children's department of the Royal Victoria Infirmary has led to the appreciation of certain aspects of this disease which it is felt are not widely known. Any factor which may lead to the delay in admission of over 24 hours is worthy of close study. In 63 children peritonitis was already present, a figure which cannot be viewed with any complacency. Comment on some of the difficulties of diagnosis in this disease has been made recently (*British Medical Journal*, 1953).

### Pathology

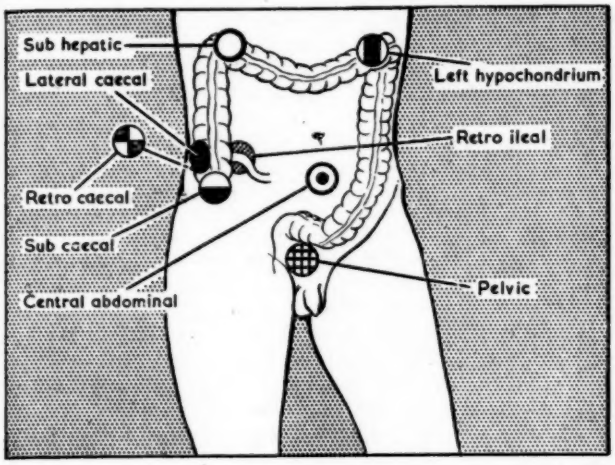
Study of the pathological lesion of the appendix in 101 cases in which this was recorded shows that an obstructive element occurred in 74. This obstruction was produced by faecaliths (32), kinking (20), and stricture (10). In 12 cases obstruction was reported, but the exact nature of this was not stated. One case of acute appendicitis was a complication of a carcinoid of the appendix which had caused some occlusion of the lumen. The high incidence of a degree of obstruction to the lumen of the appendix is to be noted, and is contrary to the experience of Bunton (1953). In many cases in which occlusion of the lumen was present it was noted that the infective process tended to stop at this point, only the distal portion of the appendix being involved in the disease process. It would therefore seem that the acute infection starts within the lumen of the appendix, and subsequently, either by tension or by spread into the walls, produces perforation. Perforation often occurs at the site where a faecalith is impacted; a faecalith causing this complication, and measuring 2 cm. in length, is shown in Fig. 1. A faecalith may be present in very young children, as was shown by one child aged 18 months.

FIG. 1.—Faecalith associated with acute appendicitis in a child of 9 years, producing obstruction of the lumen and perforation at the point of impaction.

Catarrhal or intramural appendicitis occurred in 26 cases. In this type of lesion the infection would appear to start in the wall, as commented upon by Bunton, and subsequently spread throughout the length of the appendix and sometimes on to the caecal wall. There is, however, in this series, insufficient evidence to suggest that it is possible to make a clinical differentiation of one type of appendicular lesion from another. The omentum was found limiting the spread of the infection in only 18 cases. Another variable factor in acute apendicitis is the infecting organism and its toxicity. While *Bact. coli* is undoubtedly present in most

cases, other organisms can be responsible for the disease, and variations may arise from difference of virulence as well as the factors which have already been referred to.

The position of the appendix is shown in Fig. 2, and it will be seen that in only 40 patients was it found lying in the classical subcaecal position. The development of the disease in relation to the day of admission is indicated in Fig. 3. The abscess present on the first day was due to a recurrent attack of acute appendicitis. Eight of the 21 cases admitted on the second day had already developed localized peritonitis before 36 hours. Although Bunton reports that respiratory infection is common in association with acute appendicitis, this series conforms more to the American opinion that this is not a common feature; only 14 of these children had a history of upper respiratory infection.




| | DAY OF ADMISSION | | | | | | | | TOTALS |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| ◒ | 16 | 15 | 6 | | 1 | 1 | 1 | | 40 |
| ◕ | 10 | 8 | 7 | 2 | 1 | 1 | 1 | | 30 |
| ▦ | 10 | 10 | 4 | 5 | 1 | | | 1 | 31 |
| ○ | | | 2 | | 1 | | | 1 | 4 |
| ● | 1 | | 1 | | | | | | 2 |
| ▨ | | 1 | | 1 | | | 1 | | 3 |
| ◎ | | | 1 | | | | | | 1 |
| ◑ | | | | | 1 | | | | 1 |

FIG. 2.—Position of the appendix in relation to day of admission. The circles indicate points where maximum tenderness would be expected to have occurred in first 24 hours of the disease.

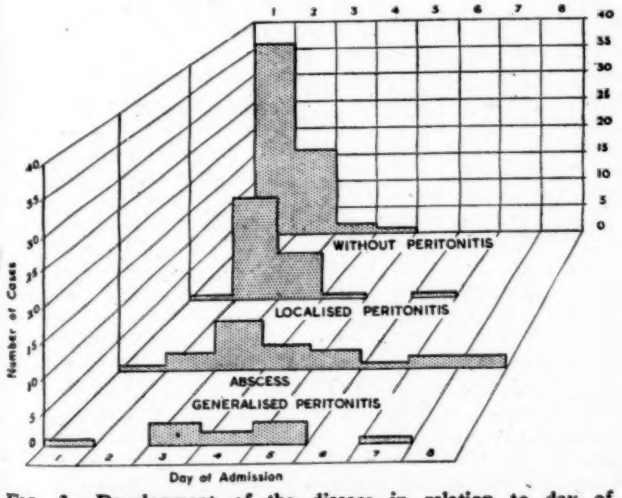



FIG. 3.—Development of the disease in relation to day of admission.

## Diagnosis

The age incidence is shown in Fig. 4. It will be seen that there are 19 cases of acute appendicitis under the age of 5 years. In view of the differences in pathology and position it is not surprising that the clinical picture of appendicitis varies greatly from case to case, and the spread of the disease process may also show considerable differences in relation to time. Localized tenderness is undoubtedly the most useful early physical sign, and Fig. 2 shows the points where tenderness could have been elicited in the early stages of the disease. Once peritonitis has developed the diagnosis becomes apparent, but it is clear that, if admission in the first 24 hours is to be obtained, rigidity should not be awaited. What can be achieved by intelligent appreciation of physical signs was well shown in one child of 15 months from whom, of course, little help could be obtained. The physician who saw the patient recognized that there was one point of maximum tenderness in the abdomen, observed by the reaction of the child to pressure over this point; and this patient is the youngest with unperforated appendix to be admitted to the department. This physician had received her training in the children's department of this hospital.

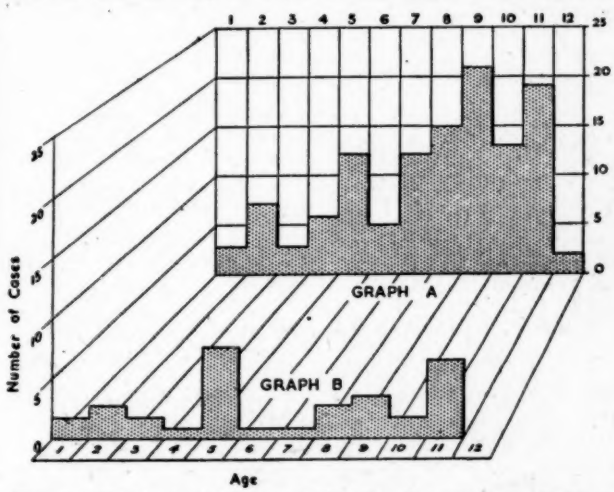



FIG. 4.—Graph A shows age incidence of acute appendicitis in this series. Graph B shows age incidence of cases in which the initial symptom was vomiting.

## Delay in Diagnosis

Factors which may lead to late admission are shown in Fig. 5. While pain is by far the commonest initial symptom, vomiting came first in 34 cases in this series. It will be seen that there was a marked tendency for patients with the initial symptoms of vomiting to be admitted somewhat later than was the case with pain. While on occasion the vomiting preceded the pain by a matter of only a few hours, this was not always the case, and in one patient there was an interval of 72 hours before pain developed. During this time vomiting had been persistent, but nevertheless the true diagnosis was not arrived at until peritonitis had developed. Another factor which may cause some delay of admission is illustrated in Fig. 2. This shows the position of the appendix in relation to the day of admission. It will be observed that in only three cases admitted after the fourth day was the appendix lying in the classical subcaecal position.

Diarrhoea is an uncommon initial symptom, occurring in only three cases, but it was an associated symptom in 19 of the 31 cases in which the appendix was found lying in the

pelvis. A child with acute appendicitis often sleeps fitfully owing to exhaustion. Professor Ian Aird (1949) stated that a child should not be wakened at night for an operation; this teaching would appear to be out of keeping with the dangers of delay, and to lull the medical adviser and the parents into a false sense of security.

Previous abdominal pain had been present in 28 cases in this series. At least some of these attacks of pain may have been associated with mild appendicitis. On several

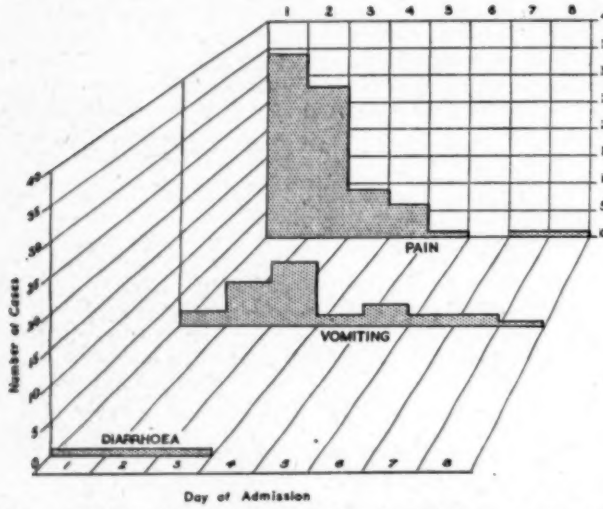



FIG. 5.—Illustrates initial symptom in relation to day of admission.

occasions these patients had been admitted to hospital and were discharged without operation. In view of the high incidence of obstructive lesions in acute appendicitis it would seem justifiable to remove the appendix when such a lesion is diagnosed in the period before the onset of acute inflammation. An observation making such a diagnosis possible in some cases was reported by me (Hindmarsh, 1948). This observation has been amply confirmed by experience and its value well established. Such lesions of the appendix also produced chronic abdominal discomfort which may simulate other disease processes, particularly in adults.

### Treatment

The pre-operative treatment of the more seriously ill patients is of great importance, and the operation should be delayed several hours to allow dehydration to be overcome. Such dehydration is due not only to vomiting and toxaemia but also, if generalized peritonitis is present, to loss of body fluids into the small intestine and into the peritoneal cavity. Once the condition of the patient has improved satisfactorily operation is proceeded with. An opportunity is also given to start streptomycin when rupture is suspected and intravenous aureomycin when generalized peritonitis is present.

*Types of Operations Performed in This Series of* 118 *Cases*

| Operations Performed | Number | Mortality |
|---|---|---|
| Appendicectomy .. .. .. | 78 | Nil |
| Appendicectomy with drainage .. | 32 | 1 |
| Drainage of abscess: | | |
| Primary .. .. .. .. | 6 | Nil |
| Complication .. .. .. | 10 | ,, |
| Interval appendicectomy .. .. | 8 | ,, |
| Total .. .. | 134 | 1 |

In 110 cases appendicectomy was performed at the first operation. A muscle-splitting incision is favoured in early cases, and was used on 57 occasions in this series; but if a mass is palpable on clinical examination and the length of the history suggests that the appendix is gangrenous and at the point of perforation, a longer incision than this is to be preferred. In this school we favour the Rutherford Morison incision, and this was used on 43 occasions. This is a muscle-cutting incision in the R.I.F. which can be extended either upwards or downwards, depending upon the position of the appendix found at exploration. In Rutherford Morison's original description the incision was much longer than is now the usual practice. The skin incision is no more than 3 in. (7.5 cm.) in the first instance, and is extended only as required. Paramedian incisions are used only when there is any doubt in the diagnosis, or when a pelvic mass can be palpated prior to operation, as in pelvic appendicitis, as this incision gives the most direct approach to the disease process. The paramedian incision was used in only 16 patients in this series.

There were 24 cases of abscess; 16 of these had the appendix removed with drainage. In six drainage alone could be instituted owing to the appendix not being readily accessible. One was treated conservatively for two to three days and subsequently drained. I would certainly agree with Deaver (1952) that there is no urgency to drain a well-localized abscess, but if such conservative treatment is adopted chemotherapy should be given. In the two other cases treated conservatively one was complicated by the presence of whooping-cough, and the risk of anaesthesia was thought to be great enough to risk delayed operation, and in the other the abscess was very well localized, with a history of six days' duration.

I agree with Gross (1953) that Fowler's position is to be recommended in cases of peritonitis, and we feel that the low percentage of subdiaphragmatic abscess recorded by the Boston Children's Hospital may be partly due to this position.

The indications for drainage are similar to those suggested by Scott and Ware (1945), of the Boston Children's Hospital, and it is only used, therefore, when a good deal of peritoneal exudation develops round a forming abscess cavity, or when it is suspected that a faecalith may have escaped from the appendix and has not been recovered. It has been the practice in this series to lay the drain down the lateral wall of the abdominal cavity into the pelvis in such cases. In no case was this responsible for post-operative obstruction, which has occurred in only one case after operation when no drain was used.

Recently there has been some discussion on the advisability of burying the appendix stump with a purse-string suture (Cleland, 1953). There was no incidence in this series, or in a much larger series in adults, in which burying the appendix led to any threatened intussusception. If the stump is carbolized an abscess in the caecal wall as reported by Cleland is unlikely to develop. When the caecum is thickened and oedematous it may not be possible to carry out invagination, and indeed it was not done in the fatal case. This child of 9 years developed a central abdominal abscess, drainage of which led to a faecal fistula, and, in spite of the prolonged administration of intravenous fluids, blood transfusion, and antibiotics, she wasted away and died eight weeks after admission. At necropsy it was shown that the appendix stump was communicating with this abscess, and it is probable that the acute pain that she developed nine days after the first operation was due to a leakage from the caecum. It would therefore seem that if for some technical reason the appendix is unable to be buried an unabsorbable suture should be used.

In the post-operative period gastric aspirations and intravenous therapy are continued in all cases of localized and generalized peritonitis. These are continued until flatus is passed or bowel movement occurs. There was no case of persistent paralytic ileus in this series.

### Antibiotics

Antibiotics were not used in cases admitted without peritonitis. These cases made a straightforward recovery, and all but one were discharged within seven days. Penicillin and streptomycin were favoured when localized peritonitis was present. This treatment is continued for five to seven

days, depending upon the patient's response. The average stay in hospital in this type of case was 14 days. In generalized peritonitis aureomycin (since it became available) was given intravenously during the time an intravenous drip was continued, unless the sensitivity of the organism called for another antibiotic. This is continued for 10 days, and is then discontinued even if the patient is febrile. The patient is not discharged until two days after the discontinuation of antibiotics, to allow any abscess to declare itself: use of antibiotics in a febrile patient tends to mask the clinical signs of the developing abscess and the abscess cavity becomes surrounded by dense fibrous tissue which makes the subsequent diagnosis and treatment more difficult. The average stay in hospital in cases of generalized peritonitis was 21 days. In some cases, however, ultimate discharge from hospital was delayed for up to two months.

When appendicectomy was not performed it was the practice to get the patient back two months later for interval appendicectomy. It is interesting to note that two cases in which an abscess was drained were readmitted with a further acute attack while awaiting interval appendicectomy. This has occurred in other cases treated by my colleagues.

Subdiaphragmatic abscesses developed in two cases—one to the left side and one to the right. One case of left paracolic abscess and six cases of pelvic abscess occurred —two of which discharged spontaneously. There were two cases in which abscesses developed deep to the wound and had subsequently to be drained. There was also the case of central abdominal abscess which has already been referred to. Wound infection developed in only six cases. It would not seem necessary, therefore, to leave the superficial layers of the wound open, as suggested by Abel and Allen (1950). None of these cases required subsequent operation, as removal of some of the cutaneous stitches usually allowed the abscess to discharge spontaneously.

### Comment

When 63 cases out of 118 are admitted with localized or generalized peritonitis the situation must give rise to great concern. It is clear that responsibility for the factors which have allowed this state of affairs to develop must be established. According to the records, in only 11 cases was failure to suspect appendicitis by the medical practitioner responsible for the delay. It must be admitted, however, that among these patients were some of the most seriously ill children. The usual tentative diagnosis had been one of gastro-enteritis, which was treated with antibiotics. In most cases, however, it is clear that the parents failed to realize that persistent pain and vomiting, particularly where the latter was the first symptom, was caused by acute appendicitis. Often, too, a parent administers a dose of castor oil or other purgative which leads to delay in seeking medical advice. A great deal can be done by education of the public, as has been shown by Abel and Allen, and it would seem that such education will be required before any marked improvement can occur in the time of admission of such children.

I agree with my colleagues in the children's department that where abdominal pain has persisted for several hours the presence of appendicitis or some other serious condition should be strongly suspected, and expert assessment made at home or in hospital as soon as possible. Our aim should be for all children with acute appendicitis to receive treatment within the first 24 hours of the disease.

### Summary

A series of 118 cases of acute appendicitis in childhood is recorded.

More than half were admitted with localized or generalized peritonitis.

Vomiting as an initial symptom occurred in 34 cases, particularly in children of 5 years and under.

Other factors which may delay diagnosis are discussed.

Treatments carried out in this series are described.

Delay in admission is mostly due to delay in seeking medical advice.

I acknowledge the assistance I have received from the ward sisters and residents in the paediatric department, particularly Dr. J. H. Jackson, whose endeavours have been largely responsible for saving a number of seriously ill children. My thanks are due to Dr. F. J. W. Miller and Dr. S. D. M. Court, who have co-operated in caring for the dangerously ill child. I am grateful for the co-operation of my surgical colleagues, and to the anaesthetists whose care has aided the smooth post-operative recovery of patients. I also thank Mr. D. P. Hammersley for the diagrams and Professor A. G. R. Lowdon for his interest and advice. I would like to acknowledge my gratitude to the late Sir James Spence for the pleasure of collaborating with his department.

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## A TRIAL OF MERCAPTOMERIN IN SEVERE CONGESTIVE HEART FAILURE

BY

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High claims have been made for mercaptomerin ("thiomerin"). In this preparation an organic mercurial compound is linked with sodium mercapto-acetate, which replaces the theophylline of earlier mercurial diuretics such as mersalyl and "unephral."

One important advantage claimed is the suitability of the preparation for self-administration by the patient in his own home (Krehbiel and Stewart, 1951). Mercaptomerin is less toxic and less irritant than mersalyl, and this permits of subcutaneous injection. Self-administration would therefore be no more onerous than with insulin. The advantages of this to both general practitioner and patient in a chronic condition like congestive cardiac failure need not be emphasized.

There is evidence, however, that non-irritant mercurial preparations may also be relatively inactive, since both their therapeutic and their toxic actions require dissociation of the compound (Handley and LaForge, 1947). The potency of all new mercurial diuretics must therefore be fully proved before their non-irritant properties on subcutaneous injection can be accepted as an advance.

A trial of mercaptomerin has been carried out in which three aspects were studied: the diuretic efficiency, the duration of the diuretic response, and the incidence of local toxic reactions.

### Methods

Patients admitted to hospital in severe congestive heart failure were used in the trial. All had marked oedema. They were given a diet constant in fluid, salt, and calorie content. Doses of 2 ml. (40 mg. of mercury per ml.) of a mercurial diuretic were given at 48-hour intervals, mercaptomerin and mersalyl being used alternately. This was continued until eight doses had been given—four of each (Fig. 1).

The diuretic response was determined by measurement of the output of urine. The volume excreted in all the 48-hour periods following the mersalyl injections was

compared with that passed in the 48-hour periods following the injection of mercaptomerin (Fig. 2). Urinary sodium studies are also being undertaken.

In order that no fluid or food was taken other than that sent from the diet kitchen, only co-operative patients were used in the trial. Further, any who lost fluid owing to vomiting or diarrhoea were excluded. Those whose salt intake had been severely restricted before admission, or

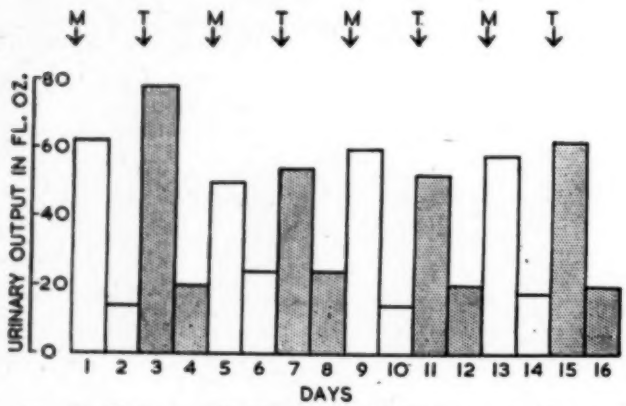


FIG. 1.—Case 2. Response to injections of mersalyl and mercaptomerin given alternately at 48-hour intervals. M=2 ml. mersalyl . T=2 ml. mercaptomerin.

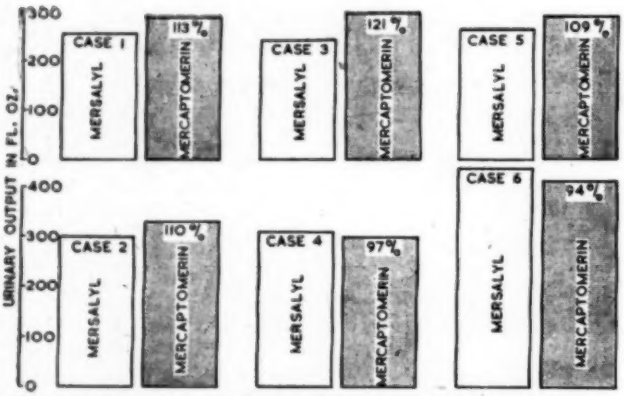


FIG. 2.—Comparison of output following mersalyl and mercaptomerin in six cases. Each rectangle represents the sum of four responses. The figures in the shaded rectangles indicate the response to mercaptomerin calculated as a percentage of the diuresis following mersalyl.

who had had intensive treatment with mercurial diuretics, were also excluded, as it was thought that the regime might cause a significant proportion to develop the low-salt syndrome. Results are available for six cases (see Table). The cause of congestive failure in Cases 1, 2, 3, 4, and 5 was chronic rheumatic heart disease; in Case 6 it was hypertension associated with myocardial damage.

All the urine passed by each patient was collected in a large pot and measured at 8 a.m. each day. At this time, on alternate days, the dose of diuretic was given. In Cases 2, 3, and 5 the first (and odd-numbered) injections of diuretic were mersalyl; in Cases 1, 4, and 6 the first injection was mercaptomerin. Mersalyl was given by intramuscular injection, mercaptomerin by the subcutaneous route.

*Response to Mersalyl and to Mercaptomerin*

| Case No. | Age | Diuresis in fl. oz. (sum of four responses) | | | | % of Total Diuresis in 2nd Day | |
|---|---|---|---|---|---|---|---|
| | | Mersalyl | | Mercaptomerin | | | |
| | | (1–24 hr.) | (24–48 hr.) | (1–24 hr.) | (24–48 hr.) | Mersalyl | Mercaptomerin |
| 1 | 36 | 166 | 89 | 196 | 92 | 35 | 32 |
| 2 | 32 | 229 | 70 | 246 | 84 | 23 | 25 |
| 3 | 29 | 163 | 79 | 163 | 130 | 32 | 44 |
| 4 | 42 | 230 | 78 | 209 | 90 | 25 | 30 |
| 5 | 51 | 174 | 90 | 196 | 92 | 34 | 32 |
| 6 | 56 | 300 | 138 | 210 | 202 | 32 | 49 |

For conversion into metric amounts: 1 fl. oz. = 28·4 ml.

The standard diet contained 40 oz. (1,140 ml.) of fluid, 1 g. of salt, and 1,300 calories. It was weighed and prepared in the diet kitchen and carried to the patients on individual trays. All the patients had been fully digitalized before collections were started, except Case 3. She was slowly digitalized during the course of the trial. Ammonium chloride was not used.

## Results

In all cases clinical improvement was observed during the trial. In Cases 1, 2, 3, and 4, slight pitting oedema was still present at the end of the trial. In Cases 5 and 6 oedema became undetectable clinically on the tenth and the eighth day of the trial respectively.

The *magnitude of the response* obtained with mercaptomerin has been compared with that from mersalyl in Fig. 2.

The *duration of the diuresis* may be inferred from the Table. In Case 3 each diuretic produced an output (sum of four responses) of 163 fl. oz. (4.6 litres) in the twenty-hour hours following injection. But in the next twenty-four hours 130 fl. oz. (3.7 litres) were secreted following mercaptomerin, whereas only 79 fl. oz. (2.2 litres) were secreted following mersalyl. It may be inferred that in this patient the mercaptomerin-induced diuresis would be more prolonged. Similarly, in Case 6 almost half the 48-hour output following mercaptomerin was passed on the second day of diuresis—a considerably greater proportion than with mersalyl.

In contrast, in the other four patients the duration of the diuresis with each compound seemed to be about equal.

The *incidence of local toxic reactions* was investigated in ward in-patients requiring treatment with a mercurial diuretic. Twenty-two patients have received 165 subcutaneous injections of mercaptomerin, each of 2 ml. The site of injection was examined by me about twenty-four hours after its administration, and again on the sixth day; and inquiry was made for pain or other symptoms. Local reactions occurred as follows:

| | | |
|---|---|---|
| Total No. of injections | 165 | |
| Average No. of injections per patient | 7 | |
| Injections followed by: | | |
| No reaction | 142 | (86%) |
| Ecchymosis | 10 | (6%) |
| Pain or discomfort lasting more than half an hour | 10 | (6%) |
| Nodule | 5 | (3%) |

## Discussion

Mercaptomerin differs from other commonly used mercurial diuretics in that theophylline has been replaced by a monothiol. (Dithiols, especially dimercaprol, are the most effective antagonists of mercury; by forming stable compounds with it they abolish both its toxic and its diuretic actions.) Combination with a monothiol greatly reduces in animal experiments the capacity of intravenous mercurial diuretics to produce myocardial damage—the acute cardiac toxicity of mercaptomerin was estimated to be a hundred times less than that of other organic mercurial compounds (Lehman, 1947). Myocardial injury is frequently a feature of severe hypersensitivity reactions to mercurials in man (Vogl, 1953), though such hypersensitivity reactions are fortunately not common. Since hypersensitivity may develop at any time during a course of mercury injections, reduced cardiotoxic properties are very desirable. Also, combination with a monothiol reduces the skin toxicity of the organic mercurial (Ruskin *et al.*, 1950), and this permits of subcutaneous injection of mercaptomerin.

Several trials of mercaptomerin have been made in American clinics, and these were authoritatively reviewed by Gold *et al.* (1952). Most of the investigators agree that the diuretic potency of mercaptomerin given subcutaneously is about equal to that of the older mercurials given intra-

muscularly; but the evidence on duration of the diuresis and incidence of local toxic reactions is conflicting.

The final trial of a drug must be carried out in all the circumstances in which it is to be used. The response of patients in severe congestive heart failure to mercurial diuretics is not infrequently life-saving, and before any new product is allowed to displace the known effective substances (such as mersalyl) in the treatment of these patients it must be proved to be at least as good in severe cases. As Modell (1944) says: "The best basis of determining the relative effectiveness of different schedules of treatment with the mercurial diuretics is the effect on the patient with a large accumulation of oedema and in congestive heart failure." Such patients are in severe failure, and since this is a dangerous state it is essential that trial and vigorous treatment go on together. It is in these patients that the method of assay suggested here seems the most suitable.

In ambulant cases able to attend hospital as out-patients the best method of assay of a diuretic is probably that described by Clarke *et al.* (1950); and DeGraff *et al.* (1936) suggest a method suitable for testing a diuretic on in-patients.

The determination of potency of diuretics by comparing single responses is not entirely satisfactory. Gold *et al.* (1952) draw attention to the variability of the diuretic response of individuals to the same dose of diuretic; and cite one patient who lost 2.5, 4, 7.3, and 2.5 lb. (1.1, 1.8, 3.3, and 1.1 kg.) following consecutive weekly injections of 1 ml. of meralluride ("mercuhydrin"). By obtaining four responses to each diuretic under comparable conditions, a much truer estimate of their value to the patient, and of the duration of the diuresis, is obtained.

It is interesting to note that the diuresis following mercaptomerin was in fact better than following mersalyl in four of the cases. But with such a variable entity as diuretic response in congestive heart failure it would require many cases, and great differences in diuretic response, to prove the greater potency of one drug over the other. It seems reasonable to conclude that in these six cases the subcutaneous injection of mercaptomerin was at least as effective as that of mersalyl given intramuscularly.

Local reactions were seen following 14% of all injections of mercaptomerin, but in almost every case these were of a minor character. Ecchymoses cleared up rapidly. Nodules were always small (approximately 5 mm. in diameter) and usually completely painless. In only one patient was pain so marked that the discontinuance of treatment with mercaptomerin was considered. However, the last nine injections received by this patient have been painless.

With the serious nature of congestive heart failure in mind, one may conclude that local reactions due to mercaptomerin have been of very minor significance in this series.

The incidence of local reactions was fully reviewed by Gold *et al.* (1952). They report the common occurrence of two varieties of local toxicity, in addition to those already mentioned: (*a*) reactions suggestive of acquired allergy (these appeared for the first time only after a considerable period of treatment, and increased in frequency or severity as the doses were continued); and (*b*) pain at the site of injection, beginning more than 18 hours after administration. It is notable that no example of either reaction was seen during the present series of injections (given in 1953), and this would seem to support the claim that the preparation now in use is an improvement on that available in 1949. This is due to the more complete removal of irritant by-products present at various stages during synthesis of the compound (H. G. Happold, 1953, personal communication).

### Summary

A method is suggested for the estimation of the relative potency of diuretics in cases of severe congestive heart failure.

In six patients with severe congestive failure mercaptomerin by subcutaneous injection produced a diuresis at least equal to that produced by intramuscularly injected mersalyl, each given in 2-ml. doses. That mercaptomerin would produce a more prolonged diuresis than mersalyl in a proportion of cases is suggested by Cases 3 and 6.

Local reactions at the site of injection of mercaptomerin have been of very minor significance.

The patients in this trial were under the care of Dr. J. A. W. McCluskie, and his encouragement and advice throughout are gratefully acknowledged. To Sir John McNee and Dr. S. Lazarus I am indebted for much helpful criticism. But for the accuracy and care of Miss McCombie, dietitian to the Western Infirmary, and the ready co-operation of the nursing staff under Sisters Brown and Calder, this trial could not have been undertaken.

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## PRIMARY SARCOMA OF THE STOMACH

BY

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Sarcoma of the stomach is rare. Snoddy (1952) concluded that the world's literature contained only 474 reported examples, including 34 of his own. The present case is added to emphasize two points—the difficulty in diagnosis and the good prognosis—and to describe the gastroscopic appearances.

### Case Report

A bookbinder, aged 47 when first seen in August, 1944, had been troubled by gnawing epigastric pain for one and a half years, and later by nausea and vomiting. Gaseous eructations "like bad eggs" had been a marked feature. Physical examination was negative. He was edentulous. He smoked four or five cigarettes a day and was teetotal. His Wassermann reaction was negative. A barium meal showed pylorospasm, and a deformed duodenal cap was seen on screening, but not on the films. A test meal revealed achlorhydria, and the vomit never contained free hydrochloric acid. The *x*-ray diagnosis of duodenal ulcer was therefore doubtful. A subsequent test meal after histamine showed acid to be present.

On gastroscopy in August, 1944, a very red and oedematous mucosa with petechial haemorrhages was seen. There was a long shallow ulcer with bright red edges at the angulus. A diagnosis of severe gastritis with superficial ulceration was made. Two months later the ulcer was smaller, but the mucosa looked the same, and there was much mucus between the folds. Vomiting had now become very frequent and he compared his stomach to a "swill tub." Visible peristalsis was seen and a diagnosis of pyloric carcinoma was considered. He was averse to operation and preferred to keep himself comfortable by washing out his stomach twice a day. Repeated swallowing of the tube made him submit readily to further gastroscopy. In December, 1944, this showed what was interpreted as an undoubted gastritis with small erosions. In February, 1945,

the appearances were much the same. There was still much pus-like mucus between the folds (see Fig.).

In April, 1945, he was investigated at the Central Middlesex Hospital. A barium-meal examination by Dr. Golding showed an enlarged stomach with much resting juice and a narrow pyloric canal. Gastroscopy showed much the same appearances as before. For the rest of 1945 and the early part of 1946 he remained fairly comfortable on a light diet. He washed out his stomach periodically. His weight was generally around 9 st. (57 kg.). Occult blood was found on many occasions. By October, 1946, he had deteriorated markedly. He was thin and apathetic. Visible peristalsis was noted and a mass was palpated in the pyloric region. Gastric lavage and intravenous infusions improved his condition. Gastroscopy on November 5, 1946, by Dr. Avery Jones showed the mucosa to be everywhere thickened and hyperaemic. On the lesser curve were patches almost like granulation tissue. The diagnosis was either a severe chronic gastritis or a low-grade infiltrating new growth.

Gastroscopic appearances in primary sarcoma of the stomach.

Laparotomy was at last agreed to and was performed on November 22, 1946, by Mr. Hugh Blauvelt. A new growth was palpated in the pyloric region. The liver and peritoneum seemed normal except for some adhesions round the duodenum. A partial gastrectomy was performed and the patient made a satisfactory recovery. A course of deep *x*-ray treatment was given, and when last seen in December, 1953, he was fit and well.

Histological section showed a neoplasm composed of uniform round or ovoid cells with numerous mitoses and a delicate pericellular argyrophil reticulum—that is, a reticulum-celled sarcoma.

### Discussion

*Diagnosis.*—In the present case adherence to the original diagnosis of severe gastritis as well as the patient's refusal of operation delayed surgical intervention considerably. More often it is clear that a new growth of the stomach is present, and then carcinoma is probable, since only 1 to 2% of gastric neoplasms are sarcomas. Differentiation can be made for certain only by histological section, and this is desirable in apparently inoperable cases of carcinoma, since should they prove to be sarcomas recovery is possible.

*Clinical Details.*—Pain is the chief symptom, and is a dull constant ache and unlike the periodic pain of ulcer. In contrast to carcinoma of the stomach, it affects young people (mostly under 50), and nutrition and haemoglobin levels are well maintained. Hydrochloric acid may be present. Occult blood is a constant finding. The growth is generally away from the pylorus and so does not usually cause obstructive symptoms as does carcinoma.

*Gastroscopy.*—The present case gave the appearance of a very fierce gastritis with giant red folds and much yellow adherent mucus between them. Persistence of such a picture should raise the suspicion that a new growth is present, particularly if the appearances are localized. The mucosa is usually unbroken, but superficial ulcers may be found (Paul and Parkin, 1944).

*X-ray Examination.*—The lesion can generally be shown to be away from the pylorus, in contrast to carcinoma, but a positive diagnosis is hardly likely. In none of the 34 cases collected by Snoddy (1952) was a correct diagnosis made radiographically.

*Prognosis.*—Of the 474 cases collected by Snoddy (1952) 50 (or 10.5%) survived for more than five years. This is very much better than in carcinoma of the stomach, in which disease Cooper (1941) reported only 4 (or 1.5%) five-year cures in a series of 264 cases. The type of sarcoma has a bearing on prognosis, since the small round-celled sarcoma has a better outlook than the other types. In addition, a sarcoma causing an ulcer or polyp is more likely to be diagnosed early than when it causes simply a diffuse infiltration.

### Summary

A case of primary reticulum-celled sarcoma of the stomach is reported. Gastrectomy was performed four years after the onset, and the patient was alive and well seven years later—that is, 11 years after symptoms began. The gastroscopic appearances are described.

My thanks are due to my wife for the gastroscopic drawing.

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## DISADVANTAGES OF THE RECTAL SWAB IN DIAGNOSIS OF DIARRHOEA

BY

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The rectal swab has been so much recommended as the specimen of choice in bacillary dysentery (Cruickshank and Swyer, 1940; Yannet *et al.*, 1942; Hardy *et al.*, 1942; Humphreys, 1944; Ferris and Fortune, 1944; Hynes, 1953) that its use has extended to less suitable diagnostic fields, although most laboratory workers now realize its limitations (Parker, 1953).

The swab is ideal for collecting material from an amoebic ulcer in the lower part of the colon through a sigmoidoscope; and, introduced into the rectum, it is a practical method of screening rapidly several hundred people (as, for instance, in residential institutions) when seeking carriers of known bacterial species, provided immediate cultivation is done.

The method goes a long way towards preventing substitution of specimens and cross-contamination by receptacles, but it is open to several objections and does not yield so high a percentage of positive results of all kinds as do whole faeces. In particular it is not satisfactory for use by practitioners in the general diagnosis of diarrhoea unassociated with widespread outbreaks of a known infection.

### Rectal Swab in Diagnosis of Diarrhoea in General

It is self-evident that the choice of a swab specimen, while permitting a bacteriological investigation (the reliability of which is discussed), excludes any macroscopic, microscopical, or chemical examination of the faeces, but it is perhaps not so generally realized how important these examinations may be.

Many specimens "negative" bacteriologically show abnormalities whose recognition is helpful clinically; and, indeed, some of these, such as worms, melaena, steatorrhoeas, and the characteristic green stool of underfeeding in infancy, may be obvious at sight. Simple microscopy yields much information in return for a very small outlay of time and materials, and would be justified if it

did no more than identify the parasite *Giardia intestinalis*, which we have found responsible for a number of severe cases of diarrhoea in adults.

The results of examining specimens of faeces sent to the Edmonton laboratory from 3,183 consecutive index cases illustrate the extent to which a complete faecal examination gives more information than can be obtained from rectal swabs. (These results will be more fully analysed in another paper. They refer to a two-year period from October, 1951. Index cases are first cases of diarrhoea from new addresses.) In this series of 3,183 specimens of faeces from cases of diarrhoea in patients of all ages which were examined by bacteriological, microscopical, and simple chemical methods, no abnormality was found in 1,605. Of the remaining 1,578 specimens, recognized pathogenic bacteria were isolated from 723, organisms of doubtful pathogenicity such as paracolon bacilli were identified from a further 229, and the remaining 626 specimens all showed abnormalities which could be demonstrated only by microscopy or simple chemical methods, for which the rectal swab is quite unsuitable. Thus protozoa and helminths were found in 213, pus (cause not found) in 186, excess fat globules in 152, red blood cells in 41, and occult blood in 34. That is to say, almost 20% of the specimens of faeces in this series showed abnormalities which could not be expected to have been demonstrated in rectal-swab specimens. A few cases of ulcer, cancer, colitis, and diverticulosis were found in this group.

To turn now to the use of swabs in bacteriological diagnosis, there is no bacteriological reason for preferring the rectal swab in infections which do not involve the rectum. In 1948 Shaughnessy *et al.*, in the United States of America, demonstrated the inadequacy of the rectal swab in salmonella diagnosis. They also examined a series of 189 typhoid contacts and found only three positive by swab, as compared with 7 by faeces. In each series the best results were obtained after saline purgation. Results may be further improved by emulsifying the faeces in saline before plating on solid media (Kroger, 1951).

A further class of organisms exists for which no comparative figures are available ; this includes the paracolons, Friedländers, and other members of the *Bacterium* group, as well as *Cl. welchii* and *Bact. coli*. For reasons of convenience swabs are often used in cholera work, but it is not suggested that they give better results than the faeces.

Swabs have been found satisfactory by Wright and Roden (1953) and others for the isolation of types of *Bact. coli* giving rise to gastro-enteritis in hospitals and nurseries, though a comparison of swab and faeces isolations has not, so far as I know, been published ; but in this laboratory, which receives specimens from cases scattered in their own homes, some swab failures have been followed by the successful isolation of O 55 and O 111 types of *Bact. coli* from the faeces. This may have been due simply to inadequate swabbing or delay before culturing, but it serves to emphasize that in general practice whole faeces should be examined.

### Rectal Swabs in Diagnosis of Sonne Dysentery

During an epidemic of Sonne dysentery in North-east London in 1950–1 it was repeatedly observed here that cultures from swabs were negative, though *Shigella sonnei* was isolated from faeces from the same patient, sometimes on the same day. No patient had a positive swab result coupled with a negative faeces culture. Cultures were made directly on Leifson's deoxycholate citrate agar, and also indirectly via selenite F broth (Leifson, 1935, 1936 ; Hobbs and Allison, 1945). This broth increased the number of successful isolations from faeces though not from swabs, and its advantage was much greater in convalescent than in acute cases. Direct plating was not discarded, because very occasionally *Sh. sonnei* grew on the primary plate but failed on the subculture from selenite. This occurred only when specimens had been collected during the first day or so of diarrhoea. Occasionally, too, growth failed or colonies were dwarfed on the plate while selenite isolation was successful. This happened when stools were fluid and very alkaline or very acid, and neutralization or dilution of such stools would overcome the difficulty. (Observation by J. H. Cowlard, working in this laboratory.)

Our experience that swabs can be very unreliable is shared by workers in other laboratories, and it therefore seems worth while to consider further the relevance of the published findings in favour of the swab to the circumstances of diagnosis in general practice.

The rationale for the use of swabs in large-gut infections is sound. Organisms producing inflammation visible through the proctoscope are more concentrated in the mucus of the wall than in the contents of the lumen of the rectum. It follows that to have any advantage over a faeces sample the swab must rub the bowel wall.

The general use of these swabs followed the publication in 1940 by Cruickshank and Swyer of a comparison of the results of faeces and swab culture in a group of children admitted to hospital suffering from acute Sonne dysentery. Swabs were taken expertly and cultured without delay on MacConkey's medium. Of the cases in which the organism was isolated from the swab the faeces cultures were positive in only 64%. About this time, however, Irons *et al.* (1939) showed that the isolation of dysentery bacilli was much more successful if deoxycholate citrate agar was used instead of MacConkey's agar, and this was confirmed by Anderson and Cruickshank (1941).

From 1940 to 1944 the swab was recommended by other writers. Papers by Yannet *et al.*, Hardy *et al.*, Humphreys, and Fortune and Ferris are often quoted, but only Yannet *et al.* (1944) and Fortune and Ferris (1945) included comparisons. They showed that, though the swab gave a 15–30% increase in isolations of *Sh. shigae* and *Sh. flexneri*, it had no advantage over the faecal specimen in their small number of cases due to *Sh. sonnei*. They worked with speculum swabs from acute cases cultured immediately on to solid media. Swabs collected in general practice, on the other hand, are subject to delays in transit to the laboratory and may not have been inserted deeply enough to begin with. Better bacteriological results have been obtained recently with serum-impregnated swabs and by placing swabs into Stuart's transport medium immediately after collection (Moffett *et al.*, 1948 ; Cruickshank, 1953).

*Delay.*—Fairley and Boyd (1943) emphasized the difficulty of culturing dysentery bacilli from old cases and from old specimens, and referred to the increasing proportion of failures if faeces were kept more than an hour or two, because of the diminution with time of the number of viable bacilli.

*Drying.*—Spicer (personal communication) has found that partial drying has a lethal effect upon *Sh. sonnei*. At cold and room temperatures he found that a reduction of the relative humidity to 30–50% produced a marked fall in the proportion of organisms viable after 24 hours. Even at a normal relative humidity (of 75–80%) the fraction surviving at the end of a week was very small. Much longer survival can occur in whole faeces, provided that containers are stoppered to prevent evaporation. *Sh. sonnei* has been cultured from faeces kept eight weeks on the laboratory bench, but, although some strains survive for weeks, others die within a few days (personal observations).

*Selective Media.*—The use of selective media that enable scanty bacilli to be found by the culture of faecal samples very much larger than can be collected on a swab has greatly improved cultural results. Citrate rosolic acid broth, a modification of Leifson's deoxycholate citrate agar, was introduced by Brodie in 1942 ; and in 1944 Jamieson *et al.* stated that 36% of the positive results from bacillary dysentery convalescents were obtained solely by this enrichment method. Selenite F fluid medium, first described by Leifson (1935, 1936), was recommended for the isolation of salmonellae by Hobbs and Allison (1945). Subsequently it was found to be useful in the cultivation of *Sh. sonnei* (personal communication from Dr. H. D. Holt) ; and in

1952, in an unpublished lecture, I described how I obtained a 26% increase in the positive isolations of *Sh. sonnei* from post-acute cases by using this medium to supplement Leifson's deoxycholate citrate agar medium. Since then Armstrong (1954) has published results demonstrating similar advantages (21–31%) in the use of the selenite medium. Cultural improvements of this order make it probable that, were a fresh comparison to be undertaken, swabs would show little if any advantage over the faeces for the isolation of *Sh. sonnei* even if the swabs were correctly taken and cultured without delay.

## Conclusion

Faeces and not rectal swabs should be the specimens of choice in the diagnosis of diarrhoea. For this purpose swabs are not adequate. The swab has a place in the investigation of outbreaks of known bacillary dysentery in institutions with laboratory facilities on the spot, but should be regarded as a preliminary to be followed, if possible, by a fuller examination of the faeces.

When considering arguments of convenience it should be remembered that the onus of collecting faeces can be placed on the patient's family, whereas rectal swabbing requires the time and skill of a qualified person.

My thanks are due to Colonel H. J. Bensted for his help during the preparation of this paper.

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The World Health Organization has published a booklet giving interpretations and instructions for coding causes of death, supplementary to those contained in the *International Statistical Classification of Diseases, Injuries, and Causes of Death*, 1948. This booklet is Addendum 1 (H.M.S.O., 1s.). Its aim is to interpret and clarify rather than to amend the classification, and in so doing to keep to what is believed to have been the original intention of the classification, avoiding changes in meaning or assignment except where they were necessitated by inconsistencies between notes or instructions or between the tabular list and the index. The booklet contains: (1) Lists of amendments to the tabular list and the index in relation to specific code numbers. (2) Supplementary rules for selection of causes of death where the certificate is not clear about which of several stated causes is the underlying cause. (3) Amendments to the intermediate and abbreviated lists. (4) Corrections of typographical errors in Volume 1 of the classification. The 1948 classification is to undergo next year a restricted revision containing these amendments, but it is not intended that the revised classification should come into use before 1958, and it is unlikely to be published for some time.

# SEVERE LOCAL AND GENERAL REACTION TO INSULIN ZINC SUSPENSION AND SOLUBLE INSULIN

BY

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AND

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A man aged 47 suffering from diabetes mellitus with ketonuria was admitted to hospital on March 31, 1954, for stabilization. He had never before been treated for this condition and there was no significant past or family history. Physical examination revealed only moderate obesity, although he had lost 17 lb. (7.7 kg.) in weight in the preceding four months. Treatment was started on January 31, 1954, with insulin zinc suspension and a diet containing 140 g. of carbohydrate. On February 5 a change to soluble insulin was made as his glycosuria and ketonuria persisted. By February 10 he was satisfactorily controlled by 30 units of soluble insulin morning and evening. All injections of insulin were given subcutaneously into his right upper arm.

During the morning of February 11 he complained of a tender irritant lump in his right upper arm together with general malaise, nausea, anorexia, and heartburn. He had vomited once during the night and had slept badly. He was not feverish, and examination showed an area, approximately 5 by 3 cm., of reddening of the skin on the outer side of his right upper arm with induration of the subcutaneous tissues. On the 12th a change to insulin zinc suspension, 60 units, was made and a single injection was given into the left upper arm. By the early afternoon a local reaction had developed at the site of injection which was similar in size to that observed in the right upper arm on the preceding day. The next day insulin zinc suspension, 60 units, was injected into the left thigh and was followed later that day by a similar local reaction. On February 14 soluble insulin, 30 units, was injected subcutaneously into the left thigh, morning and evening; local reactions of great severity followed—the entire left thigh became greatly swollen and tender, and bullae, the largest of which measured 4.5 by 2.5 cm., appeared at the site of the injections (see photograph). At the same time the patient experienced an exacerbation in his symptoms of general malaise.

Bullae at site of injections.

Treatment with promethazine hydrochloride, 25 mg. six-hourly, was started, and further injections of soluble insulin were given into the subcutaneous tissues of the anterior abdominal wall. The initial injections were followed by local reactions of little severity, and by February 18 injections of soluble insulin were unattended by any reaction and he again felt well. Treatment with promethazine hydrochloride was discontinued on the 17th, and on the 19th injections of insulin zinc suspension were started again, and have continued to the time of writing without incident.

## Comment

General reactions to insulin are not common. Jorpes (1949) quotes Allan and Scherer (1932) as stating that only

1 to 2% of all patients sensitive to insulin exhibit general manifestations. There can be little doubt that this patient's symptoms of general malaise, nausea, anorexia, and heartburn, with irregular vomiting, coinciding in onset and offset with the cutaneous reactions, were part of a general allergic reaction. This case is also interesting for the severity of the local cutaneous reaction (there does not appear to be a record of a local cutaneous reaction with bulla formation following subcutaneous injections of insulin) and the very short period of hypersensitivity.

Gastineau and Leavitt (1946) reported a case of allergy to insulin with a generalized reaction which was improved by treatment with diphenhydramine hydrochloride. In their case the reaction recurred when that drug was discontinued. In our case spontaneous desensitization probably occurred, as promethazine hydrochloride was given for only three days, and there was no recurrence when it was discontinued.

Wilder, in the discussion of the case of Gastineau and Leavitt (1946), draws attention to insensitivity to the antidiabetic activity of insulin as a form of allergy to insulin. In this case no increase in the dose of insulin was necessary during the period of allergy.

In most of the reported instances of allergic reactions to insulin it has been shown that the reactions are diminished or abolished by the use of insulin recrystallized several times, and it has been suggested that minute traces of secondary protein contaminating the purified insulin are responsible. This was probably the mechanism in our case, as a comparison of the two insulin solutions used has shown that crystalline insulin is the only substance common to both.

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# TREATMENT OF ANOGENITAL WARTS WITH PODOPHYLLIN

BY

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The treatment of soft warts in the anogenital region with podophyllin was first described by Kaplan (1942), who wrote: "The treatment . . . consists of the application of 25% podophyllin in mineral oil to all the condylomatous masses, care being taken not to make the application too liberal. Within 6 to 8 hours after the application the patient begins to experience pain over the area of application and usually requires codeine sulphate or even morphine for relief. During the next 12 hours there is a marked local reaction, with inflammation and oedema throughout the tissues near the site of application. On the second and third days the condylomata begin to slough off and the pain eases. On the fourth or fifth day the tissues return to normal. . . . A weaker solution requires repeated applications and the pain is almost as severe."

## Review of Literature

Eleven years have elapsed since that paper was published, and numerous reports have confirmed the efficacy of the treatment but stressed the frequency of reactions. Culp *et al.* (1944) treated 100 cases in the U.S. Army and 13 developed balanitis or proctitis, three of them severe enough to necessitate a dorsal slit or circumcision. Macgregor (1945) reported 25 cases in which the excess podophyllin was cleaned off with soap and water after six to eight hours, the area dried, and a dusting powder applied. In his opinion, this greatly reduced the incidence of severe reactions. Lipman Cohen (1946) treated 30 Service cases, all as in-patients. In some there was much swelling and discharge under the foreskin, which could not be retracted. This subsided with baths and 12.5% aqueous sodium sulphate dressings. The scrotum became superficially ulcerated if left for long in contact with the podophyllin. A dorsal slit and later circumcision were required in one case. In a further small series, in which the Macgregor technique was used, Cohen reported that the reactions were rather less, and remarked that "this method . . . is much less painful than Kaplan found originally, but more so than Macgregor stated."

Sullivan and King (1946) followed a similar routine, and reported that "balanitis and phimosis occur in some patients. . . . The frequency of this complication depends on the amount of podophyllin which comes into contact with the glans penis and foreskin, and also probably on individual sensitivity to the drug. The balanitis and phimosis subside in a few days if the preputial sac is irrigated daily with a mixture of equal parts of distilled water and 3% hydrogen peroxide. It is not necessary to perform a dorsal slit or circumcision except in extreme cases." Flagg and Powell (1947) experimented with various strengths of podophyllin, and recommended the use of the 25% suspension for meatal lesions, 10–15% for lesions on the glans or prepuce without phimosis or a redundant foreskin, and 5–10% for lesions under a redundant phimotic prepuce. They reported reactions in 27% of cases (non-meatal) treated with the 25% suspension. Nobis (1948) tried the effect of suspension in 96% alcohol instead of liquid paraffin, in an attempt to localize the applications to the warts and avoid the seeping which is inevitable with the oily base. Ronchese (1949) stressed the importance of ringing the area with soft paraffin, while Willcox (1948) suggested that more harm than good may result from this manœuvre.

It will be seen from this review that, although the efficacy of podophyllin has been established beyond doubt, local reactions from its use are far from negligible. Cases of severe conjunctivitis have been caused by accidental transfer of the irritant material to the eyes. There is a considerable risk that the patient who attends as an out-patient will forget or be unable to report again six to eight hours later for the removal of the podophyllin. It may perhaps be possible to avoid severe reactions by careful in-patient supervision, such as was reported by Cohen (1946). A stay in hospital, however, of between 4 and 29 days (average 12 days) seems hardly justified in the management of a comparatively minor complaint, and in civilian practice would be quite impracticable.

## New Method

It is for these reasons that the development of a safer method of treatment seems imperative. Wurm (1950) described a method in which he used a much weaker preparation, 1.5% podophyllin being dissolved in hexaethylene polyglycol, in order to get better penetration. A modification of this method has been used for the past 18 months on over 100 cases in the skin and venereological out-patient departments attached to the Royal Naval Barracks at Portsmouth.

To start with, 1.5% podophyllin in propylene glycol was used, but it has since been found that a 3% concentration is more effective, and does not cause any inflammatory reaction. The area is first cleaned with 1% cetrimide, and dried. The application is then made with an orange stick and cotton-wool, followed by profuse powdering with talc. The prepuce, if present, is then adjusted to cover the glans penis and the patient warned not to interfere with it. After 24 hours the procedure is repeated, and again on subsequent days. By the second, third, or fourth application the lesions start to melt away, and it is very seldom that more than four or five applications are required. If there is the slightest reaction, the treatment is not carried out until

it has settled, the area being kept well powdered. It is, however, very seldom that any discomfort is reported by the patient, and in no case has an oedematous balanitis developed. This really does seem, in fact, to be a safe and yet most reliable form of treatment, that can be carried out even by an untrained assistant.

It has been our experience that the harder and more chronic lesions are generally resistant to podophyllin, and usually require destruction by diathermy or electrocautery.

I should like to express my gratitude to Surgeon Commander H. L. Belcher, R.N., for his co-operation with regard to this therapeutic trial, and to the Medical Director-General of the Royal Navy for permission to publish.

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# Medical Memoranda

## Löffler's Syndrome Occurring During Streptomycin and P.A.S. Therapy

Toxic reactions encountered during treatment with sodium *p*-aminosalicylate (P.A.S.) include fever and pruritus (Hemming and Stewart, 1949), skin eruptions (Horne, 1949), haematuria (Nagley and Logg, 1949), hypoprothrombinaemia (Swanson, 1949), potassium deficiency (Cayley, 1950), and jaundice and enlargement of lymph nodes (Cuthbert, 1950). In the following case of Löffler's syndrome combined therapy with streptomycin and P.A.S. was given, the latter drug being held responsible. This is the first time, so far as I am aware, that this complication of P.A.S. therapy has been described in this country.

### CASE REPORT

An unmarried girl aged 18 suffered from tuberculous endometritis (chest *x*-ray film clear). Previous illnesses were pneumonia in 1945, and mumps and measles in childhood. There was no personal or family history of allergy. Out-patient treatment with streptomycin (1 g. daily) and P.A.S. (12 g. daily) was begun on November 18, 1952. On December 13 she complained of general malaise of three days' duration associated with anorexia, vomiting, and vertigo. She had received 25 g. of streptomycin and approximately 290 g. of P.A.S. Specific drug therapy was discontinued. After admission to hospital later the same day she had a rigor and vomited. Her temperature was 99.6° F. (37.6° C.). Her face was flushed, and the conjunctivae were injected. An intensely itching maculopapular rash quickly developed on her trunk and forelimbs. The occipital, deep-cervical, epitrochlear, and axillary lymph nodes were enlarged. There was no icterus. The liver and spleen were not palpable. Diphenhydramine hydrochloride, 200 mg. daily, was given and lotio calaminae cum menthol. applied locally. For three days she had low irregular pyrexia—99.6° F. (37.6° C.). The itching gradually subsided and the rash faded.

On December 17 she was well; the rash had gone; the liver-function tests were normal; Hb, 13.3 g.%; white cell count, 8,200 per c.mm. (differential count not performed). On December 22 the white cell count was 5,640 per c.mm. (polymorphs 53%, eosinophils nil). Diphenhydramine hydrochloride was discontinued. On the 26th streptomycin, 0.1 g. intradermally, produced generalized reaction with vertigo, tinnitus, and vomiting. Her face was flushed, there was no rash, and her temperature was not elevated. An area of induration and erythema, 3 cm. in diameter, at the site of injection later became ulcerated and persisted for two weeks.

Test doses of P.A.S., 1.5 g., 3 g., and 6 g., were given by mouth on successive days without ill effect. On January 2, 1953, a test dose of P.A.S., 6 g., was given by mouth. In the evening she complained of feeling hot, and developed a dry irritating cough. Her temperature was 105° F. (40.6° C.), pulse 120, respirations 30. Her face was flushed but there was no rash. Glands were palpable in the neck, axillae, and epitrochlear regions. The respiratory and cardiovascular systems were normal. Diphenhydramine was resumed.

Next day her temperature was normal, she felt well, and the cough was easier. *X*-ray examination of the chest revealed extensive coarse mottling throughout both lung fields, resembling a widespread bronchopneumonia. On the 4th she had no complaint; the cough was gone, and the drug was discontinued. Chest *x*-ray examination was repeated on January 8 and no pulmonary disease was seen.

Next day the Hb was 13.7 g.%; white cell count, 9,800 per c.mm. (polymorphs 70%, including eosinophils 4%). Desensitization to P.A.S. was begun according to the schedule recommended by Madigan *et al.* (1950).

January 14, P.A.S., 1.5 g.: rise of temperature in evening —100.4° F. (38° C.); shivery, but no other complaint. January 15, P.A.S. withheld; temperature normal; chest *x*-ray film showed no pulmonary disease. January 16, P.A.S. resumed at 500-mg. dose; E.S.R., 12/19 mm. (Westergren). January 18, P.A.S., 1.5 g.: well; white cell count, 10,200 per c.mm. (polymorphs 70%, including eosinophils 8%). January 22, P.A.S., 3 g.: white cell count, 10,480 per c.mm. (polymorphs 61%, including eosinophils 10%). January 29, P.A.S., 6 g.: no ill effect; cold agglutinin titre 1 in 28. February 5, P.A.S., 9 g.: no complaint; cold agglutinin titre, 1 in 16.

### COMMENT

The syndrome of acquired sensitivity to P.A.S.—namely, constitutional upset with fever and pruritic skin eruption—was first reported by Horne (1949) and has since been described and amplified by many workers. More recently (Jeffry *et al.*, 1952) it has become apparent that a similar syndrome occurring in patients receiving combined streptomycin–P.A.S. therapy may be evidence of acquired sensitivity to both drugs. The allergic nature of these reactions is indicated by the positive results of skin tests with the appropriate drug, by the eosinophilia reported by several authors, and by the effectiveness of desensitization.

There is no doubt that the above case was one of acquired sensitivity to both streptomycin and P.A.S. The main interest in the case centres on the reaction which occurred after the initial flare-up had subsided and which followed the administration of test doses of P.A.S. alone. The outstanding feature of this reaction was the absence of significant constitutional upset despite high fever (105° F.—40.6° C.). The only symptom complained of was an irritating cough which lasted nearly three days. The temperature returned to normal on the second day and remained at that level. Radiologically there was extensive patchy consolidation in both lungs, which had cleared completely five days later with no treatment other than diphenhydramine. The eosinophil count was not carried out at the height of the reaction, but one week after the onset of the reaction—that is, after resolution of the pulmonary infiltrations—eosinophils numbered 4% of 9,800 white cells per c.mm. and rose subsequently during P.A.S. desensitization to 10% of 10,480 white cells per c.mm. The occurrence in an allergic individual of such transient pulmonary infiltrations without significant general upset seems to justify a diagnosis of Löffler's syndrome.

This syndrome, as Löffler himself has pointed out, represents an allergic response of the body to an antigen, the lung being the shock-organ. In most of Löffler's cases the antigen was *Ascaris lumbricoides*, but, as Crofton *et al.* (1952) have shown in their very extensive review of the subject, a wide variety of other antigens have been incriminated from time to time. It is perhaps surprising that Löffler's syndrome is not seen more often in acquired sensitivity reactions to P.A.S. The not infrequent occur-

rence of jaundice in these reactions suggests that more often the shock-organ is the liver, probably because of the part played by that organ in the breakdown of the drug. It is, however, of interest to note that in two of the earliest descriptions of P.A.S. sensitivity reactions (Horne, 1949; Hemming and Stewart, 1949) one of the outstanding symptoms was an intractable dry cough; unfortunately, these patients were not *x*-rayed during their reactions.

The finding of cold agglutinins in the blood of the case reported above is of interest in view of the possible relationship suggested by Crofton *et al.* (1952) between Löffler's syndrome and other conditions, including tropical eosinophilia, which are characterized by the presence of pulmonary infiltrations and blood eosinophilia. Thus Viswanathan (1948) has drawn attention to the presence of cold agglutinins in the blood in tropical eosinophilia.

I wish to thank Dr. A. M. Sutherland for permission to quote from the hospital case record.

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## Embolism and Secondary Thrombosis of the Bifurcation of the Aorta

Cases of embolism and secondary thrombosis of the bifurcation of the aorta are uncommon. Patients with mitral stenosis and auricular fibrillation especially are candidates for embolism of this nature. Herrmann *et al.* (1943) gave a full review of the literature and discussed the clinical picture and treatment. They record that Fry (1939) reviewed 135 reported cases of embolism of the bifurcation of the aorta. They described five cases of their own.

When the embolus is large and the obstruction complete the clinical signs are well defined. In predisposed patients the occurrence of abdominal cramps should lead one to suspect movement of the emboli down the aorta. Lodgment of an embolus at the bifurcation of the aorta is characterized by sudden sharp pains in one leg and then in the other followed by paraesthesiae, coldness, blanching, lowered skin temperature, and absence of or greatly decreased femoral pulses. Herrmann *et al.*, however, emphasize that when the embolus is small and the obstruction incomplete a much less dramatic and less clear-cut clinical picture is presented. The length of time of survival, even after complete obstruction, the length of postponement of the development of gangrene, and the degree of gangrene are often surprising.

The following case is presented as an example of the insidious development of a clinical picture and of the possibly misleading nature of the initial symptoms and signs.

### CASE REPORT

A woman aged 38, who had been complaining for a few days of pain in the region of the fifth metatarsal of the left foot, was seen by one of us (D. F. T.) on December 19, 1949. She had a history of rheumatic mitral disease and had had a right hemiplegia due to cerebral embolism in 1946. Examination revealed no swelling or deformity of the left foot itself, and no tenderness over the metatarsal region; definite pain on straight-leg-raising of the left lower limb; tenderness over the lumbo-sacral spine; and an ill-defined anaesthesia to pin-prick over the outer part of the foot. There was no evidence of interference with the circulation of the left lower limb. A differential diagnosis of left sciatic pain due to a lumbo-sacral lesion, or early thrombosis in the vessels to the limb, was made at that stage, and the patient was admitted to hospital. *X*-ray examination of the lumbo-sacral region showed no abnormality. She was kept under observation and at first there was no change in her condition.

On December 28 tenderness over the metatarsal region of the foot was still present and there was also tenderness over the external popliteal nerve at the neck of the fibula. Straight-leg-raising on the left was still limited and painful, and the pain was felt in the foot. However, it was noted that, though the colour and temperature of the left foot were normal at rest, the foot became a little pale and cold after it had been moved passively for a few minutes. Mr. W. H. Bailey, who saw the case by request at this stage, agreed that no active treatment was indicated. On the following day the patient complained of increasing pain. Besides the pain in her leg and foot she also had pain in the left iliac fossa and left lumbar region. No pulse could be felt in either lower limb. There was tenderness in the left iliac fossa and in the left lumbar region. Her pulse was increasingly rapid. Later that day there was mottling of both lower limbs. Her respirations became rapid and laboured. She was obviously in severe pain. The following day she died.

*Post-mortem Examination.*—The body was well nourished. There was slight wasting of the right arm and leg, and some swelling of both ankles and feet. The right ventricle was moderately enlarged and hypertrophied. The left auricle was dilated and hypertrophied. The cardiac muscle was quite firm. The mitral valve was funnel-shaped, its orifice being extremely stenosed, the dimensions being approximately 1.5 cm. by 3 mm. There were no vegetations on the valve or on the posterior wall of the left auricle, nor were there any thrombi in either auricles or ventricles. In the aorta, from the level of the left renal artery to the bifurcation, was a firm ante-mortem thrombus which was firmly adherent to the wall of the vessel. A similar adherent thrombus was present in the left renal artery, and the smaller tributaries of the aorta. Below the bifurcation of the aorta, a recent red ante-mortem thrombus extended down the common iliac and into both external and internal iliac arteries. There was no atheroma of the aorta, its branches, the coronaries, or cerebral vessels.

Both kidneys presented many deep scars, the result of multiple infarction. The left kidney, with the exception of a small area at the inferior pole, presented the picture of recent complete infarction. The right kidney also contained a number of small recent infarcts. The spleen was deeply scarred and distorted and, if anything, was smaller than normal. The liver showed several large areas of congestion, the appearances of which were in keeping with recent infarcts. Both lungs showed large areas of collapse.

On opening the dura an encysted collection of cerebrospinal fluid was present over the left parietal lobe. Dissection of the brain revealed a large cyst of the left cerebral hemisphere occupying a subcortical situation, extending down to and destroying the internal capsule, and passing from the anterior part of the occipital lobe to the posterior part of the frontal lobe. Clearly this was the end-result of the infarction of three years ago.

*Conclusion.*—Mitral stenosis, hypertrophy of the right ventricle, infarction of the brain, liver, spleen, and kidneys, pulmonary collapse, embolism of the aortic bifurcation, and subsequent thrombosis of the aorta. The embolus was probably derived from a thrombus formed on the mitral valve, although there was no evidence of the thrombus formation on the valve when examined on the table.

Our thanks are due to Miss Jean Evison for her help in the preparation of this report.

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# Reviews

## TECHNIQUES IN VIROLOGY

*Techniques de Laboratoire Appliquées au Diagnostic des Maladies à Virus.* By P. Lépine and R. Sohier. (Pp. 479; 39 figures. 2,400 fr. or 3,000 fr.) Paris: Masson et Cie. 1954.

Despite the growing number of textbooks and popular accounts of viruses there are at hand few adequate descriptions of the techniques and methods employed in virus diagnostic work. This book aims at providing for this need, and, though it necessarily reflects the preferences of its French authors, most beginners will be glad to have it.

The book is divided into two parts. The first deals with such subjects as the collection of specimens from patients, the maintenance of virus strains, and various diagnostic tests such as complement-fixation and methods of isolating viruses. In this part there is a tendency to describe too many variants of the same procedure, but on the other hand the accounts of the breeding and use of laboratory animals cannot readily be found elsewhere.

The second part of the book, twice as long as the first, deals with laboratory methods used in the diagnosis of particular virus infections. Since many of these diseases can be accurately diagnosed on clinical grounds alone, the authors have listed the type of case in which the clinician may usefully seek laboratory aid. Thus mumps infection may present as orchitis, meningo-encephalitis, or pancreatitis without any obvious involvement of the salivary glands. The tests which can help in this and in other infections are described in great detail and the interpretation of findings is discussed at some length. As one might expect from the authors' wide experience, the laboratory aspects of rabies is one of the best chapters, while that on smallpox is among the least satisfactory. Now that simple and reliable methods are available it is time that recommendations for the inoculation of suspected variolous material into rabbits and monkeys, and the discredited Paul's test, found their way out of textbooks. In general, however, the advice given is reliable and clearly set down, and if, as in the chapter on poliomyelitis, the information is sometimes a little behind the times, this, as the authors point out in their preface, is welcome and indeed essential in any rapidly expanding science.

A. MACDONALD.

## LUMBAR DISK LESIONS

*Lesions of the Lumbar Intervertebral Disc: With Special Reference to Rupture of the Annulus Fibrosus with Herniation of the Nucleus Pulposus.* By R. Glen Spurling, M.D. (Pp. 140+xi; 77 illustrations. 34s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. Toronto: The Ryerson Press. 1953.

This monograph is one of a lecture series, the author being the professor of surgery (neurosurgery) in the University of Louisville School of Medicine, Kentucky. It is of interest that this experienced surgeon has dedicated the book to Mixter, a prominent surgeon with similar specialist interests, and to Barr, a leader of orthopaedic surgery in Boston.

It was written with the object of correlating the pertinent anatomical, physiological, and pathological aspects of disk lesions with the clinical features, and giving an outline of the management of the condition resulting. This object is achieved, and the author has enhanced the value of the monograph by avoiding the temptation to write a lengthy treatise. In fact, he gives much useful information in a concise and practical form.

The consideration of this very specialized subject is largely from the neurosurgical point of view. The author states where his opinion differs from that of orthopaedic surgeons, but he has no hesitation in valuing that of Barr and others. This is not a book on backache, and its appeal to the general practitioner in Britain will be limited. There are instructive chapters on the embryology, anatomy, physiology, and pathology of the lumbar disk. The details of the annulus fibrosus and nucleus pulposus and its herniation are clearly described. The remarks on lumbar puncture being a possible aetiological factor in disk injury and disease are important.

The description of the clinical picture is orthodox and adequate. Details of methods of examination are precise, and the author emphasizes the value of accurate observations. The part played by radiography and myelography in diagnosis is recognized, and a number of excellent illustrations add to the value of the description. In the chapter on therapy spinal fusion and post-operative pain are discussed. There is an analysis of the results of different types of treatment. There are ample references to literature, most of the articles being written by neurosurgeons. The publishers aid the pleasure of the reader, as the paper, printing, and illustrations are excellent.

ST. J. D. BUXTON.

## ALCOHOL ADDICTION

*Chronic Alcoholism and Alcohol Addiction.* A Survey of Current Literature. By R. J. Gibbins. (Pp. 57. No price.) Ontario: Alcoholism Research Foundation. 1953.

This short survey of modern views on alcoholism is concerned largely with problems of aetiology and treatment. The author considers aetiology from a wide variety of approaches, and gives a critical review of social, cultural, constitutional, and psychological factors in the development of addiction. The role of cultural factors is emphasized in an interesting comparison of the varying incidence of alcohol addiction in different racial, religious, and social groups. There is general agreement that alcohol addicts contain a high proportion of psychiatrically abnormal personalities, but there is doubt whether the abnormalities present are primary or secondary, and whether there exists a specifically predisposed personality. The author suggests that a possible solution of this last problem might be found in the study of those personality factors which differentiate addicts from non-addicts within groups characterized by a high (and, it might be added, low) incidence of alcohol addiction. The results of treatment do not favour any single method to the exclusion of others, with the possible exception, admittedly in a selected group, of the wide social approach of Alcoholics Anonymous, of which an excellent account is given. This book is refreshing in its broad approach and critical evaluation. There is a bibliography of nearly 200 references.

R. T. C. PRATT.

## CERVICAL SPINE

*Die Halswirbelsäule: Pathologie und Klinik.* By Dr. Med. Gerhard Exner. Introduction by Professor Georg Hohmann. (Pp. 140; 42 illustrations. D.M. 21.60.) Stuttgart: Georg Thieme. 1954.

This monograph on the cervical vertebrae gives an excellent account of the anatomy and pathology of this region of the spine, of the variations which occur, and of the clinical syndromes which arise from disease and injury. The author confines himself almost entirely to conditions arising from the bones themselves and only incidentally refers to the vast problems arising in the complex nervous and vascular structures to which they are related. But in this limited field he gives accurate and useful information on methods of investigation, abnormalities, and pathological processes. The book is evidently the result of intense study and wide experience in a difficult subject, it is well arranged and produced, and it deserves the close attention of all those who are interested in the many problems which arise in relation to the cervical spine.

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## DECLINING TUBERCULOSIS MORTALITY

No great changes of mortality from tuberculosis occurred in this country between the end of the Stuart period and the beginning of the nineteenth century,[1] and in London about one death in five was due to this scourge. About the middle of the century, when Villemin was establishing that the disease was due to a specific infective agent, deaths in England and Wales averaged 65,000 per year in a population of less than 20 millions. Since then, apart from temporary setbacks during the two world wars, improvement has been continuous, and by 1948, with the population more than doubled, deaths from tuberculosis numbered 22,000. Some of the credit for this great decline can be attributed to treatment, sanatorium and surgical, and some to the isolation of infectious patients, but the main factor has been improvement in standards of living—better nutrition, better housing, better working conditions. The relative importance of various social and environmental factors has been studied recently in London by Benjamin[2] and in Glasgow by Stein.[3] That socio-economic factors are still important has once more been demonstrated in the Registrar-General's latest occupational mortality analysis,[4] which shows that the tuberculosis death rate in 1950 of men in social class V (unskilled occupations) and of their wives still remained twice as high as for those in social class I (professional occupations).

Since 1948 treatment with new drugs—streptomycin, P.A.S., and derivatives of isonicotinic acid—has converted the long and steady retreat of tuberculosis deaths into a sudden rout, and in 1953 deaths in England and Wales numbered only 9,000. In Scotland, where mortality continued high for some years after the 1939–45 war, similar improvement has now occurred, and Ruys[5] and McDonald and Springett[6] have shown that this experience has been shared throughout Western Europe. The degree of improvement has been remarkably uniform, and in many countries only two-thirds as many people died from tuberculosis in 1952 as in 1950.[7] In England and Wales the death rate per 100,000 fell from 37 to 24, in Scotland from 54 to 31, in Northern Ireland from 48 to 30, in the Irish Republic from 78 to 54, and even in Portugal, outstanding for its high mortality, the rate fell from 142 to 96. Across the Atlantic the United States death rate during the same period declined from 27 to 16.

The sex–age pattern of mortality in England and Wales presents a number of well-recognized but unexplained features.[8] In women highest rates are among young adults, and have remained so for many years. In men the highest rates a century ago were in young adults, but since then there has taken place a gradual advance in the peak age, which is now in the neighbourhood of 60. This has revived interest in the "cohort" method of studying tuberculosis mortality rates, and Springett[9] has suggested that the high death rates of older men at the present time derive less from contemporary circumstances than from the adverse conditions that affected this cohort of men when they were young. Another departure from the conventional approach has been adopted by Logan and Benjamin[10] in the concept of mortality measured not in numbers of deaths but in numbers of potential years of life lost. In 1952 tuberculosis accounted for 2.1% of all deaths, but for 5.7% of years of working life lost.

Though mortality has been declining fast there has been no corresponding diminution in numbers of tuberculosis notifications, and this has aroused much speculation and not a little concern. The lowest annual total of notifications recorded was 46,000 in 1939. This rose to 51,000 in 1941 and was still 48,000 in 1952. There is reason to believe, with Lowe and Geddes,[11] that the maintenance of a high notification rate is the result of more effective and earlier case-finding; but with the numbers of tuberculosis survivors now increasing so fast year by year the possibility cannot be ignored that the proportion of potential disseminators of infection may be rising despite the fact that in many cases the sputum becomes free of tubercle bacilli under chemotherapy.[12]

Part of the difficulty in assessing the significance of the present paradoxical fall in mortality with no corresponding reduction of notifications arises from the inadequacies in the existing notification procedure, in that insufficient provision is made for obtaining details about the nature and severity of each case. In an effort to obtain fuller information a form of "Intimation of Tuberculosis" has been introduced

[1] Greenwood, M., *Epidemics and Crowd Diseases*, 1935, London.
[2] *Brit. J. Tuberc.*, 1953, **47**, 4.
[3] *Brit. J. soc. Med.*, 1952, **6**, 1.
[4] *Registrar-General's Decennial Supplement: England and Wales, 1951. Occupational Mortality, Part I*, 1954. H.M.S.O., London.
[5] *Docum. Med. geogr. trop.*, 1953, **5**, 271.
[6] *Brit. med. Bull.*, 1954, **10**, 77.
[7] *W.H.O. Epidemiological and Vital Statistics Report*, 1953, **6**, 125.
[8] McDonald, J. C., *Brit. J. soc. Med.*, 1952, **6**, 259.
[9] *Lancet*, 1952, **1**, 521, 575.
[10] *Monthly Bull. Minist. Hlth (Lond.)*, 1953, **12**, 244.
[11] *Brit. J. prev. soc. Med.*, 1953, **7**, 227.
[12] *Memorandum on Prevention of Tuberculosis*, 1954, London.
[13] *Scottish Health Bulletin*, 1954, **12**, 21.
[14] *Amer. Rev. Tuberc.*, 1953, **68**, 1.

in Scotland for use in the hospital service.[13] This form is supplementary to statutory notification and is required for each patient newly diagnosed as suffering from active tuberculosis. It will be sent to the medical officer of health and will supply information about B.C.G. vaccination, contact, method of discovery, radiological and bacteriological findings, and disease classification. Central analyses of the data will be carried out. In England and Wales there are schemes for the central registration and follow-up of patients suffering from cancer and, quite recently, of patients in mental hospitals, but there are no similar arrangements on a national scale for tuberculosis. Such a central register operating during the course of the past twenty years might have been able to shed much light on current problems; and it is worth considering whether it might not be usefully introduced even now. So long as notifications remain at their present high level without our knowing whether we are delving more and more into the reservoir of active cases that would hitherto have gone undetected or whether notifications are simply keeping pace with an undiminishing number of new cases, we must not assume, from the recent landslide in deaths, that the reign of the captain of the men of death is at last over. Tuberculosis, as Dubos[14] has remarked, is not an inescapable component of human society. It is a social evil which can and must be stamped out.

## HORMONE THERAPY OF ULCERATIVE COLITIS

Chronic ulcerative colitis continues to be a most serious and baffling illness. The aetiology is unknown, although infection, allergy, enzyme derangement, hypermotility, hypoproteinaemia, and psychoneurosis may all be contributing factors. On occasions it would appear that it is a systemic disease with diffuse involvement of almost any system of the body. Treatment remains largely empirical. Elsewhere in this issue we publish two papers on the use of corticotrophin (A.C.T.H.) and cortisone in this disease. The opening paper, by Dr. S. C. Truelove and Professor L. J. Witts, is a preliminary report of a large-scale trial of cortisone at different centres in this country: it is the largest objective investigation of its kind in this disease yet published, and the authors and their collaborators are to be congratulated on the excellent planning of this research. The second paper, by Drs. A. P. Dick and A. G. Beckett, is a detailed account of fourteen cases treated with A.C.T.H. Both papers confirm previous reports that hormone therapy has a definite but probably limited place in the treatment of this condition. The best results are seen when the disease is not too far advanced, but is active and giving rise to severe systemic reactions.[1] The effects of treatment are to increase the appetite, restore a sense of well-being, decrease faecal blood loss, and greatly reduce the number of bowel movements. Hormone therapy is also a valuable preoperative measure for critically ill, exhausted, or debilitated patients, whose condition may be improved sufficiently to allow elective surgery.[2] The correct dosage of these hormones depends on the duration and briskness of the disease and the responsiveness of the adrenal glands. Gray[3] has suggested that spontaneous remission in this disease may depend in part on the release of endogenous hormones. Most authorities[1–5] agree that hormone therapy is less effective when the disease is of long standing. Pathological changes in the bowel wall are then often severe, and the bowel is grossly foreshortened and rigid from large amounts of fibrous tissue deposition: the lumen is markedly diminished, and the mucosa has a cobblestone appearance with deep-seated, long, narrow striations. The bowel contents rush through this diseased colon like water down a waste pipe. Invalids with severe chronic ulcerative colitis feel themselves social pariahs, and are often in a psychological tumult from the effects of the disease. Fortunately surgery can often transform them into healthy and happy members of the community.

Treatment with A.C.T.H. and cortisone is not without danger. Massive haemorrhage, perforation, and peritonitis have all been reported.[6 7] Dick and Beckett report on one patient who developed marked adrenal insufficiency at the start of A.C.T.H. therapy, and Wilson and Roth[8] describe a patient who developed a massive adrenal haemorrhage (found at necropsy) just after the cessation of treatment. The periodic use of cortisone might well prevent adrenal exhaustion during A.C.T.H. therapy. On the other hand, prolonged administration of cortisone may depress endogenous A.C.T.H. production, a process which may be reversed by alternating A.C.T.H. with cortisone. Eliot and Giansiracusa[4] found no evidence of tissue inactivation when using purified preparations of A.C.T.H. even after twelve or more months of continuous administration. Tuberculosis and past or present symptoms of peptic ulcer are contraindications to hormone therapy (the co-

[1] Kiefer, E. D., and Elliot, J. M., *Gastroenterology*, 1954, **26**, 29.
[2] Hamilton, E.C., and Carlson, R. I., ibid., 1954, **26**, 734.
[3] *J. Amer. med. Ass.*, 1952, **148**, 1489.
[4] Elliot, J. M., and Giansiracusa, J. E., *New Engl. J. Med.*, 1954, **250**, 969.
[5] Wirts, C. W., Rehfuss, M. E., and Yantes, H. A., *J. Amer. med. Ass.*, 1954, **154**, 36.
[6] Pessel, J. F., Beairste, E. B., Edwards, M. H., Rathmell, T. K., and Wise, J. S., *Amer. J. dig. Dis.*, 1953, **20**, 318.
[7] Tulin, M., Kern, F., and Almy, T. P., *J. Amer. med. Ass.*, 1952, **150**, 559.
[8] Ibid., 1953, **152**, 230.
[9] Halstead, J. A., *et al.*, *Gastroenterology*, 1954, **26**, 65.
[10] Du Toit, C. H., and Bauer, W., *Proceedings of First Clinical A.C.T.H. Conference*, 1950, Philadelphia.

existence of peptic ulcer and ulcerative colitis is not as uncommon as was once believed[9]). It is still not known whether long-continued treatment restrains the illness and halts the pathological process sufficiently to leave a useful colon, nor whether it diminishes the incidence of complications such as haemorrhage, stricture formation, and perforations. It may be that hormone therapy controls the salient symptoms of the disease but does not reverse the essential pathological process. Only time can show whether this is so. Bauer's[10] analogy about the place of these hormones in the treatment of rheumatoid arthritis may also apply in ulcerative colitis: the flame of the gas burner is put out by A.C.T.H. or cortisone, but the remaining pilot light flickers low to ignite the disease as soon as the hormones are withdrawn. The future progress of the cases now reported will be awaited with great interest. The period of two and a half years, the longest time in Dick and Beckett's series, is too short for any final appraisement in a disease in which relapses may occur at long intervals.

## HERPES SIMPLEX

One of the commonest of human infections, herpes simplex is usually associated with the recurrent cold sore or fever blister. But in 1938,[1] after the recognition that many cases of ulcerative stomatitis in young children were herpetic in origin, a new interest was taken in the relationship of this virus to human disease. Two distinct types of infection were soon recognized[2]: a primary infection occurring in persons with no antibody, sometimes resulting in a systemic illness, and the recurrent form in which a purely local lesion develops in those previously infected. As a result of improved techniques for the study of viruses in recent years the diagnosis of herpetic infection has become relatively simple,[3] and in two recent reviews McNair Scott[4] and his colleagues[5] at the Children's Hospital in Philadelphia, the centenary of whose foundation is to be celebrated next year, show how extremely diverse may be the ways in which herpes presents in practice.

Primary herpes simplex is essentially a disease of young children, and considerable variation is seen from case to case. Inapparent infection is much more common than clinical disease, which is not altogether surprising in view of the ubiquitous nature of the virus and the degree of parasitism it has achieved in man.[6] In the Philadelphia series[5] less than 1% of children under observation had symptoms; similar findings have been reported from Britain.[7] However, when conditions are favourable for dissemination of virus, both incidence and effect may be much greater. Outbreaks of stomatitis in institutions are well recognized, and in one instance reported by Anderson and Hamilton[8] the attack rate was 100%, with clinical stomatitis in more than half the patients. Similarly, outbreaks of generalized herpes infection occur in children's skin wards and can be of serious consequence. Serological tests show that nearly all newborn infants are protected by maternal antibody for four to six months,[5] and that 60% of children have had their primary infection by the time they are 5 years old.[5]

The characteristic vesicular lesion of herpes simplex may develop anywhere on the skin or mucosal surface, but the most frequent sites are on the face and in and around the mouth; less commonly a vulvovaginitis is seen.[4] Herpetic infection of superficial grazes, knife cuts, and burns may give rise to difficulty in diagnosis, not only because of the unusual sites but because of the accompanying induration. In a typical case of primary herpes simplex the constitutional reaction may be out of all proportion to the extent of the lesions. Pyrexia and enlarged regional glands are early features of the infection, and these conditions are invariably prolonged when secondary bacterial infection occurs. Eczematous children, or others with an abnormal skin, may develop a generalized infection (eczema herpeticum). Some of the aspects of this condition have been discussed by Dr. G. I. Barrow in a recent issue of this *Journal*.[9] As a result of haematogenous and surface spread, crops of vesicles, invariably umbilicate, appear over a wide area of skin.[10] The general appearance of these patients, with the accompanying toxaemia, suggests an acute exanthem; not all, however, are severely ill. In a series reported by Jackson and Dudgeon[11] seven of the sixteen cases were classed as mild; but they were still infectious. Encephalitis may develop as a direct result of virus dissemination,[4] but in addition primary herpetic infection of the central nervous system presenting as an aseptic meningitis has been described.[12] An even more severe type of infection has recently been recognized by Zuelzer and Stulberg[13] in the form of a fulminating neonatal infection. Several of the infants affected

[1] Dodd, K., *et al.*, *J. Pediat.*, 1938, **12**, 95.
[2] Burnet, F. M., and Williams, S. W., *Med. J. Aust.*, 1939, **1**, 637.
[3] *British Medical Journal*, 1952, **2**, 1349.
[4] *New Engl. J. Med.*, 1954, **250**, 183.
[5] *J. Pediat.*, 1952, **41**, 835.
[6] Burnet, F. M., *Virus as Organism*, Harvard Monograph Series, Cambridge, Mass., 1945.
[7] Spence, Sir James, *et al.*, *Thousand Family Survey, Newcastle.* Quoted by Scott.[5]
[8] *Med. J. Aust.*, 1949, **1**, 308.
[9] *British Medical Journal*, 1954, **1**, 482.
[10] Brain, R. T., *et al.*, *Brit. J. Derm.*, 1950, **62**, 203.
[11] *Gt. Ormond Str. J.*, 1951, **1**, 125.
[12] Afzelius-Alm, L., *Acta med. scand.*, 1951, Suppl., **263**, 1.
[13] *Amer. J. Dis. Child.*, 1952, **83**, 421.
[14] France, N. E., and Wilmers, M. J., *Lancet*, 1953, **1**, 1181.
[15] Pugh, R. C. B., *et al.*, *Arch. Dis. Childh.*, 1954, **29**, 60.

were premature, and visceral necrosis was a marked feature at necropsy. Similar cases have been described in Britain.[14 15]

At present no chemotherapeutic agent has any specific action against the virus of herpes simplex, but owing to the early and in many cases gross secondary infection, particularly in the generalized form, it is advisable to use chemotherapy to control secondary invaders. The choice will depend on the organisms and their sensitivity. In certain instances when infants, known to be susceptible, are exposed to infection or likely to be so, temporary passive immunization with gamma globulin should be considered.

## COMPLICATIONS OF DIABETES

The complications of diabetes may be divided into three main groups—ketosis and coma, infections, especially tuberculosis, and what Joslin[1] terms cardiovascular–renal diseases. The first and second of these should be preventable or at least amenable to treatment. The third group consists of degenerative lesions affecting the eyes (in addition to cataract), the kidneys, the heart, and the limbs: their serious clinical manifestations include retinopathy and blindness, renal failure, ischaemic heart disease and hypertension, gangrene, and neuropathy. These to-day account for no less than 75% of deaths among diabetics,[1] and Dolger's findings suggest that the young patient may have to expect the onset of such complications after 15–25 years of diabetes,[2] the danger being greater if the disease is inadequately controlled.[3] In recent years much thought has been given to the question of dietary control in their prevention, and this is the problem that Professor D. M. Dunlop examines in an extract from his Lumleian Lectures published at page 383.

There are two schools of thought about dietary control in the treatment of diabetes—those who advocate a "free diet," with its psychological benefits, and those who stress the need for strict control (not more than 250 g. carbohydrate a day) in order to reduce hyperglycaemia and hence complications. In 1951 Dunlop and his colleagues[4] reported that 39 out of 50 patients had been satisfactorily maintained on a "free diet" for five years. It is as well that no definite conclusions were reached, because a further four years have now elapsed and the results, in his own words, "have been disastrous." Nine patients have developed tuberculosis and 18 degenerative complications, from which 4 have already died. Since 11 patients had already been removed from the series because of deterioration in their diabetic state, only 9 can be considered as entirely satisfactory. A further 167 patients who had attended as out-patients over a period of 15–30 years were analysed according to the state of diabetic control. There are drawbacks to this method of assessment,[5] but the incidence of complications, especially neuropathy, was undoubtedly greatest in those who had been poorly controlled. These results have convinced Dunlop that the prime duty of the physician in charge of diabetics is to enforce strict control.

It is nevertheless distressing to find well over half the "good control" group with complications, and this has been the experience of others. The aim of treatment, in our present state of knowledge, is to maintain the blood sugar at a normal figure, but the disorder of carbohydrate metabolism is only one aspect of the syndrome of diabetes mellitus. Vascular disease, particularly of the retina and kidneys, is another, and the term "degenerative complications" is perhaps misleading. More research is needed into the pathogenesis of these disabling lesions so as to settle once and for all the doubts about dietary control.

## OCULAR DISCOMFORT AT THE CINEMA

The popularity of television has led to attempts by the cinema industry to attract the public by innovations such as 3D, Cinemascope, Cinerama, and other wide-screen devices. 3D is a form of stereoscopic projection of cinema pictures intended to give the illusion of "depth." This is attained by the projection of two pictures, one representing the right-eye image and the other the left. Means must be provided to enable each eye to receive its appropriate image, and the method usually adopted is to polarize oppositely the light beams forming each picture, so that when a spectator wears spectacles which are also oppositely polarized the left and right eyes will receive only their appropriate images. The same end may be achieved less delicately by a development of the anaglyph, in which the two pictures are viewed through red and green spectacles after an initial projection through colour filters of red and green. Two systems of stereoscopic projection which do not require spectacles are in use in Russia: these depend on the division of the picture on the screen into vertical strips by wire or prismatic "rasters," so that by keeping the head still it is possible for right and left eyes to see only alternate strips of screen. Such a scheme has the disadvantage of more than halving the accommodation of the auditorium. Large-screen presentation aims at realism by more nearly filling the spectator's field of vision. Cinerama achieves this by a system of multiple projectors. Cinemascope depends on the use of very wide angle photography, and the image is compressed by a special lens into a normal 35-mm. film frame. By the introduction of a special complementary lens in the projector the image is laterally expanded to its original proportions and fills a screen the width of which is 2.6 times its height. Other less effective systems simply depend on increasing the magnification of an ordinary picture and cutting off its top and bottom edges.

These new cinematic devices are gradually finding their own level in the world of entertainment now that their initial novelty is wearing off. Meantime medical men

[1] Joslin, E. P., Root, H. F., White, P., and Marble, A., *The Treatment of Diabetes Mellitus*, London, 1952.
[2] *J. Amer. med. Ass.*, 1947, **134**, 1289.
[3] Root, H. F., *Amer. J. med. Sci.*, 1949, **217**, 545.
[4] *British Medical Journal*, 1951, **1**, 1095.
[5] Tunbridge, R. E., *Lancet*, 1953, **2**, 893.

are being increasingly asked whether these new methods of presentation cause "eyestrain." This popular term has acquired emotional overtones and should be quietly discarded by the medical profession, and perhaps replaced by the term "ocular discomfort." Among the lay public there is a widely prevalent idea that by excessive use of the eyes some irreparable damage may conceivably be done. This is of course not true, except when some definitely nocuous agent is the cause—as, for instance, unphysiological exposure to light is the cause of eclipse blindness. Ocular discomfort may result from undue dazzle, excessive use of the ciliary muscles, or faulty muscle balance. The new cinematic devices do not appear to cause discomfort by dazzle. The effort of concentration on the screen, with overuse of the ciliary muscles, may lead to headache. 3D films are apt to cause headache because of faulty muscle balance, as with excessive convergence. Looking at a wide screen from the cheaper seats may result in ocular discomfort because of the unusual angle of vision. Such effects as there are on the eyes are transitory, and there seems little danger of adverse complications. It would be wise to restrict the seating at children's matinées to those parts of the auditorium allowing good stereoscopic reception. Uncomfortable conditions for adult customers carry their own corrective, in so far as the public will presumably refuse to patronize such entertainments.

## RADIOSENSITIZERS

If a drug is to be of use as a radiosensitizer in practical radiotherapy at least three criteria must be met. First, the drug must accentuate the effect of ionizing radiations so that either the cure or palliation aimed at can be achieved with smaller doses of radiations or, in the extreme case, a radio-resistant tumour might be rendered radiosensitive; secondly, the action of the drug must be more pronounced in tumour than in normal tissue; and, thirdly, the drug must be well tolerated by the patient and should have no permanent effect on normal tissue cells.

A programme to aid the development of an efficient radiosensitizer has been in progress at Cambridge since 1946, and much attention has been given to compounds related to tetrasodium 2-methyl-1 : 4-naphthohydroquinone diphosphate ("synkavit"). These compounds have been found to have no toxic effects on animals, including man, and, *in vitro*, on cultures of chick fibroblasts—these last experiments showing that the compounds are potent inhibitors of mitosis with only transient effects on resting cells.[1-3] The action of such drugs in potentiating the anti-mitotic and chromosome fragmentation effects of 220 kV *x* rays has been clearly seen in tissue cultures[4]; for example, the effects produced by small doses (150 r) of *x* rays in conjunction with synkavit ($2 \times 10^{-6}$ molar) are much more than the additive effect of *x* rays (300 r) and synkavit ($4 \times 10^{-6}$ molar) acting separately. To show potentiation of *x* rays in their action on tumour-bearing rats is technically more difficult. However, a large-scale experiment has now been completed and intravenous synkavit, followed 30 minutes later by *x* rays, is clearly more efficient in producing tumour retrogression than either *x* rays alone or, an even better control, than *x* rays and intramuscular synkavit.[5]

A method of finding out whether a drug has a more pronounced effect on tumour than on normal tissue is to see whether it is found in greater concentration in the tumour than elsewhere. After intravenous injection of small amounts of synkavit or related compounds into a rat with a Walker carcinoma, it is possible to show selective concentration in the growing edge of the tumour (and in some other organs) of an ultra-violet fluorescent derivative of the injected material.[5] A series of studies with various isotopically labelled compounds has confirmed, for the most part, the results of the fluorescence experiments.[6]

The clinical trials of these compounds at Cambridge have been designed to give a statistically significant quantitative result as convincingly as possible with the minimum number of patients, and, at the same time, to be completely acceptable from the moral and ethical point of view. Early trials showed that the compounds used alone had no therapeutic effect on malignant tumours, but that when used in conjunction with *x* rays an improved clinical response occurred more often than expected. The full trials began early in 1951. Cases were allotted at random (with the aid of a table of random numbers) to one of two alternative forms of treatment: *x* rays with intravenous synkavit (X+I.V.S.) or *x* rays with intramuscular synkavit (X+I.M.S.), the latter being regarded as the control group. At the same time it was essential to provide for each patient that form of treatment which was considered the best possible in the light of present knowledge. Thus it was often necessary to depart from the theoretically ideal form of experiment with deliberate sacrifice of information. Results[5,7] of the first 91 cases of inoperable carcinoma of the bronchus show that the two groups are substantially identical in composition, and that, while the mean survival time after first treatment has been shown by other groups of workers[8] to be about 4 months with *x*-ray treatment only, X+I.M.S. gave a mean survival time of 6 months, and X+I.V.S. about 11 months. The improvement is in agreement with clinical impressions, and it appears justifiable to conclude that intravenously injected synkavit has a small but useful effect as a radiosensitizer in the radiotherapy of inoperable carcinoma of the bronchus.

Mitchell's early reports[9-11] have been criticized,[12] but other workers[13] appear to confirm them. It is of the utmost importance, therefore, that as many other clinical investigators as possible should set up this type of trial.

[1] Mitchell, J. S., and Simon-Reuss, I., *Nature, Lond.*, 1947, **160**, 98.
[2] Friedmann, E., Marrian, D. H., and Simon-Reuss, I., *Brit. J. Pharmacol.*, 1948, **3**, 263.
[3] ——— ——— *Biochim. biophys. Acta*, 1952, **8**, 680; and 1954, **13**, 260.
[4] Mitchell, J. S., and Simon-Reuss, I., *Brit. J. Cancer*, 1952, **6**, 305, 317.
[5] Mitchell, J. S., *Acta radiol. (Stockh.)*, in the press—1953 Congress Volume.
[6] Maxwell, D. R. Presented at the Second Radioisotope Conference, Oxford, July, 1954.
[7] Mitchell, J. S., *Brit. J. Cancer*, 1953, **7**, 313.
[8] Ariel, I. M., Avery, E. E., Kanter, L., Head, J. R., and Langston, H. T., *Cancer (N.Y.)*, 1950, **3**, 229.
[9] *Brit. J. Cancer*, 1948, **2**, 351.
[10] *Experientia (Basel)*, 1949, **5**, 293.
[11] *Annual Report British Empire Cancer Campaign*, 1949, **27**, 214; 1950, **28**, 213; 1951, **29**, 190.
[12] Gellhorn, A., and Gagliano, T., *Brit. J. Cancer*, 1950, **4**, 103.
[13] Berkman, A. T., *Türkiye Tip [Encilmeni Arsivi*, 1951, **2**, 1; and private communications.

# PAEDIATRICS OF THE PAST

## A NOTE ON PRACTICE OVER THE PAST 60 YEARS IN THE QUEEN ELIZABETH HOSPITAL FOR CHILDREN

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On looking through the old records of this hospital we noted many interesting features of children's diseases. Records have been found from as early as 1885, and we are fortunate in having 198 actual case notes written by house-physicians and house-surgeons in 1893.

The hospital was founded by Dr. and Mrs. Nathaniel Heckford in 1868. The original premises were in an old sail-loft at Ratcliffe Cross, but in 1877 the hospital was formally opened on its present site—being then known as the East London Hospital for Children and Dispensary for Women. Until the beginning of the second world war the hospital had between 100 and 140 beds. There were roughly 1,500 admissions a year, and all types of cases were taken, including diphtheria, typhoid fever, whooping-cough, and often measles. When practicable, these obviously infectious cases were sent to fever hospitals, but more often than not they were nursed in special wards in the hospital.

During the second world war the area surrounding the hospital was heavily bombed; indeed, the hospital itself suffered severe bomb damage and many records were lost. The surrounding area is now largely depopulated and the hospital no longer caters for the same numbers as in pre-war days.

### Case Histories for 1893

The 198 case histories for the year 1893 show that all the patients were admitted under the care of Dr. Eustace Smith, who was senior physician for 40 years, until his death in 1913. Most of the histories concern patients over 2 years of age. There are very few on infants under a year, and very few on fatal cases, so that these particular case notes are not representative of the period as a whole. However, many of them are interesting and instructive. Among the diagnoses included in the notes are: croupous pneumonia, pleuropneumonia, bronchopneumonia, pleurisy, pulmonary tuberculosis, tuberculous peritonitis, empyema, influenza, enterica, diphtheritic paralysis, renal calculus, tetany, rickets, and jaundice.

The case histories are short and to the point. Past history and family history are nearly always noted, with particular reference to a family history of tuberculosis; but social history is never mentioned. Progress notes, besides referring to the clinical condition, often record the food eaten and the nature of enemata given. Drugs used in the treatment are rarely mentioned, and this is in accord with the views of Dr. Eustace Smith on the value of drug therapy in disease in children. In his book *A Practical Treatise on Disease in Children*, published in 1889, he writes: "In the matter of treatment, it has been the aim of the writer to emphasize the value of diet and judicious nursing in the cure of disease, and to allot only a secondary place to the actual administration of physic." In the same book there is some excellent advice regarding measles: "It is not necessary in cases of measles to keep the child dirty."

With regard to the physical examination there is usually a detailed description of the pulse, and in the presence of heart disease the cardiac outline on percussion is noted, as well as the presence of murmurs. Physical examination of the lungs is described very carefully and in great detail, rubber stamps of the chest often being used to depict physical signs. Abnormal findings in the abdomen are fully described, but rectal examination is not mentioned. There is seldom any information on the extremities and the central nervous system. In cases of fever the skin texture is often recorded.

The use of the ophthalmoscope is noted on one occasion. The urine was sometimes tested for albumin, and occasionally examined microscopically in cases of nephritis. Other pathological investigations are not recorded, but in one case of fibroid phthisis it is stated that tubercle bacilli were found.

Temperature charts are attached in every case, and were printed by Wertheimer Lee and Co., E.C.2. These charts are much the same as any other Rigden chart, and only the temperature is shown in graphic form. A note is made of pulse and respiration at the bottom of the chart. Temperatures were taken at 2, 6, and 10 o'clock during the day and night in pyrexial cases, and twice a day in afebrile patients.

A number of cases of rheumatic fever are reported. The terms mitral stenosis and aortic incompetence are not used, but when the heart was affected the diagnosis was morbus cordis or mitral and aortic disease. Salicylates were used for rheumatic fever, and a favourite prescription for rheumatic heart disease was:

| | |
|---|---|
| Tinct. ferr. perchlor. .. .. .. | m xv |
| Tinct. strophanth. .. .. .. | m iv |
| Glycerin. .. .. .. .. | m xv |
| Aq. chlorof. .. .. .. .. | ad ʒss |

t.d.s. post cibos.

Some vivid progress notes are present regarding a child with rheumatic heart disease with failure. On January 9, 1893, it was noted that "five leeches were applied, but did not bite well . . . on two previous occasions, when the pulse and right heart were failing, great benefit was obtained by injecting

| | |
|---|---|
| Liq. strychnin. .. .. .. .. | m iii |
| Vin. gallici .. .. .. .. | m xx." |

On February 4: "Child had an attack of hurried breathing . . . and extremely weak flutter pulse. Was given hypodermic of strychnine and brandy, amyl nitrite also to inhale, and improved. . . . At night she had another attack, and was leeched on the right heart. In the morning 260 oz. fluid aspirated from abdomen with much benefit." July 1: "Discharged. A well-marked systolic and presystolic bruit at apex conducted in to axilla and up toward base, where it gains again in intensity over sternum between second cartilages."

One lad is described with what was probably Fallot's tetralogy. A good account is given of his cyanosis, clubbing, and precordial murmur.

The case of a boy of 9 years with chronic diarrhoea is mentioned: "Two years ago he had measles, and diarrhoea ever since . . . up to ten motions daily—very offensive. Vomiting during the last two years—wasting. . . . Pale and rather wasted child . . . the abdomen is distended and doughy: skin inelastic. Nothing abnormal felt . . . the thumbs and great toes are in the position of tetany." This may well have been a case of coeliac disease, as it was recognized at the time not to be tuberculous peritonitis.

The only surgery noted is rib resection for empyema. The anaesthetic used was chloroform, and from the accounts it appears to have been quite satisfactory. The average stay in hospital for a case of empyema with rib resection was two to three weeks, although some cases were kept in the ward or a convalescent home for a few months.

It is interesting to note that in nearly every family at least one child had died; for example, a boy of 9 admitted

with influenza : "Three brothers and sisters died of diphtheria and one at 14 days of weakness." A boy of 2 was admitted and died of rickets : "Eight other children, of whom five were dead." Girl of 8 with pneumonia : "Third child of seven, all but this and one other died when babies with convulsions and diarrhoea."

### Analysis of Morbidity and Mortality

The figures and statistics in this section have been obtained from three sources : from the annual reports of the resident medical officer for 1885–7 and 1893–1925 ; from the in-patient register for 1937 and 1938 ; and from case notes for 1949–51. In this analysis all tonsillectomy admissions have been excluded.

Total mortality figures are shown in Fig. 1. An interesting feature is the gradual decline in mortality after the first world war to a very low level in 1937–8.

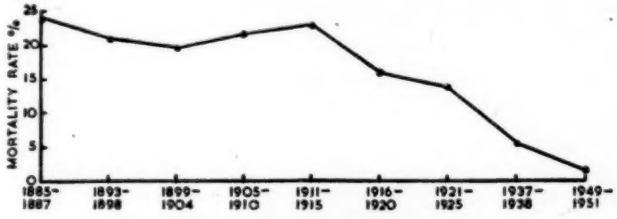


FIG. 1.—Mean mortality rate.

Study of the morbidity and mortality figures over the years in question reveals much that is well known, and perhaps a little that is not so well appreciated. Therefore only a few conditions are dealt with in some detail, in order to illustrate points of interest.

### Pneumonia

The number of admissions of all forms of respiratory diseases has tended to remain constant, usually in the region of 20–30% of all cases admitted to hospital. Pneumonia commonly accounted for just over half of all patients admitted with respiratory diseases. Mortality figures in pneumonia are dealt with under different age groups. Fig. 2 illustrates the mortality in infants under 2 years, and Fig. 3 in children of 2 years and over. In children over 6 years pneumonia has a negligible mortality. In this age group, from 1893 to 1905 the mortality was but 5%. This illustrates the observations of Dr. Eustace Smith, who, in his book *On the Wasting Diseases of Infants and Children*, published in 1876, writes as follows about lobar pneumonia : "Primary croupous pneumonia requires little medicine : the treatment should be rather directed to ward off disturbing influences than by injudicious meddling to interfere with the course of the disease, the tendency of which is to recovery." In the early years R.M.O.s constantly emphasized the difference between croupous pneumonia and bronchopneumonia. Babies with bronchopneumonia often had a mortality as high as 80%.

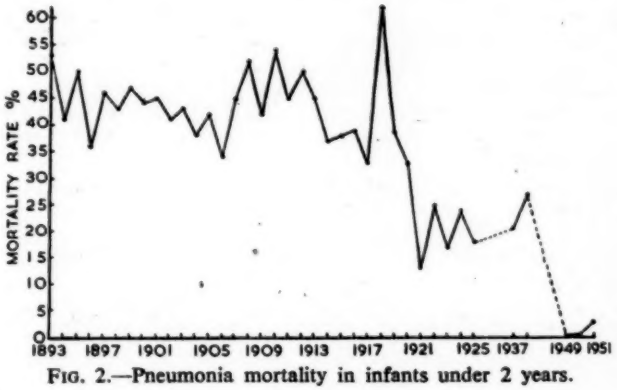


FIG. 2.—Pneumonia mortality in infants under 2 years.

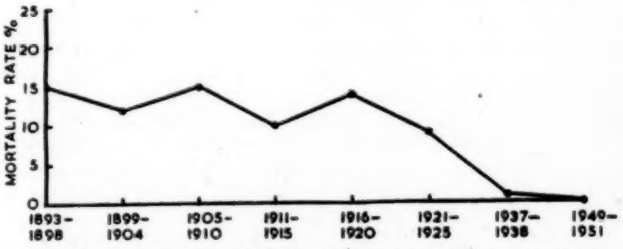


FIG. 3.—Pneumonia mortality in children aged 2 years and over.

Already, prior to the antibiotic age, pneumonia in children of 2 years and over had ceased to be a killing disease ; but in infants under 2 it still had a high mortality. In this group it was commonly 40–45%, with a peak during the influenza epidemic of 1918. After the first world war the mortality declined to half its previous level, and in the antibiotic age the mortality from pneumonia in infants is virtually nil.

### Gastro-enteritis

This is almost entirely a disease of infants under 2 years, 100 to 200 cases having been admitted annually. The disease was always referred to as summer diarrhoea, and was more prevalent in hot summers. The largest number of cases on record (253) were admitted in the year 1911, in which the summer was the hottest ever known. In that year the R.M.O. writes : "With the extreme heat of summer came a correspondingly heavy outbreak of infantile diarrhoea. Both in extent and severity the disease was considered by those longest connected with the medical wards to be exceptional."

The mortality rate of gastro-enteritis in infants is shown in Fig. 4. In nearly every annual report the R.M.O. commented on gastro-enteritis and its inevitably high mortality. "It may be noted that the mortality in 164 cases of epidemic diarrhoea treated in the year 1906 is 46.3%. This compares favourably with the death rate of 57.8% in similar cases treated in 1905." In the past three years the mortality has been greatly reduced, and in fact the disease seems to be dying out, the summer epidemics having already ceased by 1937.

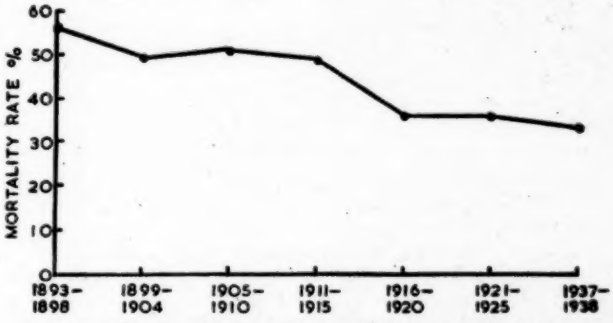


FIG. 4.—Gastro-enteritis mortality in infants under 2 years.

### Whooping-cough

In 1896 the R.M.O. writes : "For about twenty years successive resident medical officers had hoped that whooping-cough wards might be added to the hospital . . . whooping-cough is stated to be the third most fatal disease in childhood, the annual mortality from this cause in Great Britain being over 190,000. Patients suffering from this disease are not admitted to the fever hospitals. . . . I hope that means may be found of finding beds for some of these unfortunate children."

Some nine years later a whooping-cough ward was opened, and thereafter R.M.O.s continually noted in their reports the high mortality in infants. In the years 1905–9 there were 289 cases of whooping-cough in infants, 129 of which were fatal.

### Diphtheria

Half a century ago this was a very common disease, accounting for about 10% of all admissions. Most of these were transferred to isolation hospitals, but of the more severe cases, those that were unfit to be moved, some 20 a year died here.

The disease occasionally spread to the staff : " During the year (1893) three nurses and a ward maid contracted diphtheria, but in each case recovered. A laundry-maid also contracted the disease, which I regret to say proved fatal." Antitoxin therapy was introduced in 1898 : " In several cases of very severe laryngeal diphtheria, the injection of antitoxic serum, I am convinced, prevented operative interference."

### Miscellaneous Conditions

Typhoid fever, congenital syphilis, infantile marasmus, rickets, and urinary calculi, formerly all very common, are now very rare. Infantile tetany has almost disappeared, and the last case of laryngismus stridulus was seen as far back as 1910. The first case of coeliac disease was recorded in 1901. Then there is a lapse of some 20 years before two further cases were so diagnosed. Its incidence increased, but latterly the disease has again become uncommon, and in the past three years only seven cases of coeliac disease have been diagnosed at this hospital, whereas nine cases of fibrocystic disease of the pancreas have occurred.

Tuberculosis is decidedly less frequent, and the incidence of rheumatic fever and chorea appears to be decreasing. Both the incidence and the mortality of pyogenic meningitis are much lower. The serious blood dyscrasias have always been rare—even recently ; and, interestingly enough, clinical scurvy has always been very uncommon—only two or three cases having been admitted annually in the early part of this century. Diabetes has also been consistently rare.

With regard to some surgical conditions, pyloric stenosis was first diagnosed at necropsy in 1901. The first operative recovery was in 1909. Intussusception had a mortality rate of about 30% before the first world war. Thereafter it gradually declined until in 1937–8 it was virtually nil. It is interesting that for the past 60 years the annual incidence of intussusception has remained fairly constant. Appendicitis was first recorded in 1897 (four cases—no deaths). Prior to this it appears to have been diagnosed as typhlitis and perityphlitis.

The incidence of otitis media remained fairly constant over the past 50 years, but mastoiditis has decreased sharply since 1937. Admissions for tonsillectomy, however, remained constant at 300–450 from 1921 to 1951. The first note on tonsillectomy was in 1911, but adenoidectomy was recorded in 1893. Osteomyelitis was previously common, 20–30 cases a year being admitted. In the past three years there have been only three cases of osteomyelitis.

### Summary

An account is given of the history of the Queen Elizabeth Hospital for Children in the East End of London, of its associations with Dr. Eustace Smith, and of some of his writings.

Records of morbidity and mortality have been found from 1893 to 1925. These have been studied and contrasted with similar records from 1937 and 1938, and with records from 1949, 1950, and 1951. These show some of the changing patterns of diseases of childhood over the past 60 years.

We should like to thank the consultant staff of this hospital for their interest, and Dr. I. M. Anderson in particular for making available to us the early publications of Dr. Eustace Smith.

## CLINICAL FORUM AT THE CIBA FOUNDATION

### OSTEOARTHRITIS OF HIP

The second of a series of informal discussions on controversial clinical problems was held at the Ciba Foundation on July 1. With Dr. BASIL KIERNANDER in the chair, Professor J. TRUETA opened a discussion on the treatment of osteoarthritis of the hip. He had believed until recently that in this condition pain, sclerosis, and ischaemia went together. Recent work at Oxford, however, had shown that there was a hyperaemia of the femoral head in this condition, which, he believed, followed a disturbance of weight-bearing in this region. The main causative factor in osteoarthritis was probably a defective blood supply to the articular cartilage. Osteoarthritic changes were first noticed in the non-weight-bearing part of the head upon which intermittent pressure was not exerted. This, Professor Trueta thought, was essential for the proper nutrition of cartilage in the hip-joint. The success of any operative procedures employed would depend upon the extent and success with which the hyperaemia was reduced and the weight-bearing corrected.

Mr. K. I. NISSEN felt that Professor Trueta's work would simplify the whole problem of surgery of the osteoarthritic hip, and after reviewing the various procedures available concluded that in England there should be a return to those of the simpler type. Dr. H. A. BURT pointed out that osteoarthritis of the hip was by no means always accompanied by symptoms: in 100 necropsies 60% of the cases were found to have arthritic changes, but only 3% were known to have had symptoms. The physician could help by: (1) relieving pain (often analgesics are not used sufficiently); (2) increasing mobility ; (3) increasing muscular development ; (4) improving function by the use of appliances and trick movements ; and (5) correcting posture. It was important to treat the patient as a whole and not the pain. When symptoms got out of control and the patient went rapidly downhill despite a full physiotherapeutic regime, then it was time to pass the patient to the surgeon.

#### Operative Treatment

Mr. JOHN CHARNLEY, speaking of monoarticular osteoarthritis, said that he now used a central displacement type of arthrodesis in which the head of the femur was passed through into the pelvis, with the femoral neck taking the weight directly from the acetabulum. Where the aim was having bony union he also used a screw compressor. However, bony union was poor, and fibrous ankylosis was the usual result. With this operation the hip was painless, and a plaster spica was needed for only four to six weeks. The result of fibrous union appeared to be as good as that of osseous union. Since the femoral neck was placed through the acetabulum, external rotation was prevented, only a short hip spica was needed, and knee mobility was retained.

In the discussion which followed Professor TRUETA said that he considered that both unilateral and bilateral cases were mechanical in origin to the extent that the cartilage was not up to its responsibility. Mr. Charnley's operative successes he thought were due to reduction in the hyperaemia following the correction of mechanical errors. Procaine injections he considered relieved the pain by reducing the hyperaemia. The emphasis in physical medicine, which at the moment was placed upon the muscles, should rather be upon the cartilage.

Dr. E. G. L. BYWATERS thought that the blood-vessel response was not necessarily primary and that the earliest degenerative change in the cartilage was where the cartilage itself was at fault. Mr. W. A. LAW thought that conservative methods must have the first place in the treatment of this condition, but that few patients had the benefit of a regime such as Dr. Burt had described. Arthroplasty must still have a place in the treatment of bilateral cases where the patient through necessity must remain fully mobile. The

most important points in a cup arthroplasty were scrupulous technique and thorough aftercare. Full muscle control was more important than a wide range of movement.

Dr. F. S. COOKSEY said the most important aim in conservative treatment was to retain a full range of movement, and hence early diagnosis was of importance. Good results could be attributed to providing a wider area of cartilage for weight-bearing. Dr. G. D. KERSLEY, Dr. OSWALD SAVAGE, and Mr. CHARNLEY also joined in the discussion.

# Nova et Vetera

## THE EARLIEST PRINTED MEDICAL BOOKS

The process that we call "printing," by which we normally mean printing with movable types, began in Europe at some time near 1450. Printing without movable types is much older; indeed, impressing from inscribed seals goes back 5,000 years and more, while printing on textiles was common for hundreds of years before the fifteenth century. Even the printing of texts, as in "block-books" cut in reverse on a sheet of wood which was then inked and pressed on paper, is known from the fourteenth century. The use of stamps for the impressing of the initials of paragraphs in manuscripts is perhaps earlier still.

Printing with movable type is said to have been invented in 1041 in China, and later was familiar there. In our Middle Ages it spread westward from China to the Moslem Near East, where, for reasons that are not clear, it offended religious feelings and was suppressed. How far it continued to be secretly practised, and whether and to what degree the craft reached Europe from Islam, is altogether obscure.

The stages involved in the development of the craft of true printing in Europe have themselves yielded an immense and controversial literature. From it there emerges the near certainty that, for effective purposes, the first Western practitioner of the art was Johann Gutenberg (*c.* 1400–68), of Mainz, or at least a firm to which he belonged. The first printed book that carries a date is the Mainz *Psalter* of 1457, which bears the name of Peter Schöffer, son-in-law of Gutenberg's ex-partner and then enemy, Johann Fust (died 1467). Gutenberg is said to have begun printing with movable type between 1444 and 1448. Much of this is in dispute, but it is certain that there were several printers at work at Mainz when the sack of the city in 1462 dispersed them and their types and machines over Europe. There are records of 51 printers in Germany and 73 in Italy, and smaller numbers in France, Flanders, Britain, and Spain, before 1500. It is estimated that this second half of the fifteenth century produced about 8,000,000 volumes, a greater number than all the scribes of Europe had launched in the previous 12 centuries, since Constantine shifted the seat of his Empire from Rome to Byzantium in A.D. 330, about the time that the codex or book finally displaced the roll or scroll.

### Incunabula

For bibliographers, book collectors, and librarians, books printed before 1500 have long had a special attraction—some might call it a dangerous fascination. One of the largest collections of medical *incunabula*, as these works are called, is in the Wellcome Historical Medical Library. Mr. F. N. L. Poynter, its librarian, has just issued his long-looked-for catalogue of them.* It is admirably conceived, executed, and illustrated, and is in every way worthy of the great institution from which it comes. However, a catalogue, and especially a catalogue of printed books, is peculiarly resistant to lively treatment in review. We therefore pay Mr. Poynter's work a greater compliment by considering medical incunabula as a whole, for they cannot be studied seriously without reference to the magnificent collection in his charge.

The word *incunabula* may not be familiar to all readers in all its aspects. It is, in classical Latin, a neuter plural devoid of a singular, and means "swaddling-clothes," being based on *cunae*, a feminine plural, equally without a singular, meaning "cradle." By easy transference incunabula came to mean "infancy" and was used by German writers of the late eighteenth century for the infancy of printing, arbitrarily dated as ending in 1500. A necessary but technically unjustifiable singular, "incunabulum," was formed to signify a book printed in the fifteenth century. This word in due course gave birth to the unlovely offspring "incunable," which we must accept into the English language with as good grace as we may.

But, the reader may ask, why end the incunable period at 1500? Why indeed? Alas! it is irrevocable, for every great library long ago accepted it. The choice is not only arbitrary but inconvenient: 1480, 1490, or 1510 would have been historically more workable. For medicine, 1500 is specially unlucky, because the Revival of Learning was later for the medical than for the literary classics, and the early years of the sixteenth century are here peculiarly interesting. However, it is useless to cry over curdled milk: we must accept the date and rejoice that some, at least, of the early medical books have been scientifically explored. And so to the medical incunables themselves.

The first bit of medical printing known is a Kalendar for 1457 in Gutenberg type. It was discovered in 1803 in a register of accounts in the Mainz archives, and is now in the Bibliothèque Nationale at Paris. Its medical interest is that it gives certain days as most suitable for purging or bleeding. A number of such leaflets are known, and they may be classed, along with plague tractates, astrological forecasts, charms, prayers against pestilence, and the like, as semi-medical. The first medical book by an Englishman to be printed was the *Rosa Anglica* (Pavia, 1492) of John of Gaddesden (1280?–1361). He was physician to Edward II, a Prebendary of St. Paul's, and perhaps the original of Chaucer's "Doctour of Physicke." It is unimportant even among mediaeval medical works, and it has been described, not wholly unjustly, as "a scentless English rose." The first English printer, Caxton, was not interested in medicine, and the first pseudo-medical work that appeared in English was "A Litil Boke the whiche traytied and reherced many gode thinges necessarie for the [Fever] Pestilence" by one described as the "Bishop of Arusiens," wherever that may be. It was very badly printed in London in or about 1485, and the only surviving copy is in the John Rylands Library at Manchester.

Nowadays we think of printing primarily as a means to convey something novel—news, information, literature, discoveries, etc. Our press, in its various forms, provides authors with a mechanism for publicity. Yet it took long for the early printers to see their craft in that light. The first medical author to see his own work in print was Paolo Bagellardi (died 1492), of Padua, where he professed first philosophy and then medicine—a common combination in those days. His book, a very true incunable, was appropriately *De infantium aegritudinibus et remediis*, "On diseases of infants and their treatment" (Padua, 1472).

The Middle Ages had produced a wealth of medical literature which, whatever its faults, contained some good pieces. The *Chirurgia* of Guy de Chauliac, the *De juvamentis membrorum* by some unknown thirteenth-century compiler, the *Anatomia* of Mundinus, and the *Liber de febribus* of Isaac Judaeus are not wholly contemptible. Guy and Mundinus did not get into print until 1478 and the other two until much later. Such examples could be multiplied indefinitely. On the other hand, even the early period of printing did produce two ancient classics of the first rank that had remained unknown to the West since ancient times. They were destined

**A Catalogue of Incunabula in the Wellcome Historical Medical Library*, by F. N. L. Poynter (Librarian). For the Wellcome Historical Medical Museum by the Oxford University Press, London. 1954. Small 4to, pp. 16+160, with 12 plates.

to provide the very foundations of scientific medicine, Aristotle in theory, Celsus in practice.

### Aristotle and Celsus

The Latin Middle Ages had built their faith largely on what they supposed to be the works of Aristotle. Yet they had never possessed any of his works in the original and few in any translation direct from the original. This, for the biological sciences, was righted once and for all in 1476, when there appeared at Venice the superb volume *De animalibus*, translated direct from the Greek by the Italianate Greek, Theodore of Gaza (fl. 1430–80). The wealth of sound observation and fine reasoning in this noble volume provided a firm foundation for the rise of scientific biology in the following century. This was a work addressed to all men of reason. But a work calling physicians in particular back to common sense and experience was Celsus's *De medicina*. It first appeared in print at Florence in 1478. The text had been unknown to the Middle Ages, and the manuscript containing it was discovered shortly before it was printed. From then on it provided the best and sanest standard of medical practice for many a long day.

### Centres of Printing

The last twenty years of the fifteenth century produced far more printed books than the previous thirty. If the general standard did not rise it is at least true that there then became available many more medical books of historic importance than in the previous period. There is still a significant dearth of books bearing the names of Galen and Hippocrates, who did not come to their own till the sixteenth century was well advanced. But the printing and distribution of books had, by now, become an important industry. Where were these books printed and why were they printed there? To help answer these questions, Mr. Poynter provides an index of presses. Venice comes very easily first. Her printers produced more than four times as many medical incunables as all the other printing centres in Europe together. Rome, Bologna, and Florence follow at a long distance. In the German-speaking area Strasbourg comes first, Basle, Cologne, Augsburg, and Nuremberg making a fair showing. No other centre, in or out of Italy or Germany, is worth considering on a numerical basis. Why were these towns so supreme in the early medical book trade?

Omitting Rome and Florence, which have special literary histories, and neither of which was ever again prominent in the trade, the answer seems clear. The main difficulty of the trade was transport. It was the era of the folio and the quarto—the octavo, an Aldine novelty of the next century, had not yet appeared. To convey a thousand folio volumes, each of which might weigh 10 lb. or more, over the tracks that then did service for roads was a formidable undertaking. The alternative was water transport. Venice had here an immense advantage. She had the largest mercantile marine in the world, her ships sailed to every European port, and her waterborne traffic extended into North Italy along the River Po. Moreover, from Venice there was an easy land way to Vienna and the Danube basin and a well-worn and familiar track to Basle and the Rhine basin. From Basle most of Central Europe could be reached, and notably Strasbourg and Cologne, and so out into the sea, North-west Europe, and the Hansa towns. Cologne, still a free city, was the busiest entrepôt of Northern Europe. Venice herself, outside the control of Pope and Emperor, had, moreover, the two greatest medical schools of her day, Bologna and Padua, within easy reach by water. It was no accident that medical books were first printed at such centres. And, looking at the matter in reverse, it was no small thing for the medical schools of Bologna and Padua that such centres of printing and distribution were accessible to them.

CHARLES SINGER.

# Reports of Societies

## NEUROCHEMISTRY

[FROM A SPECIAL CORRESPONDENT]

The First International Neurochemical Symposium recently held at Magdalen College, Oxford, is the latest venture sponsored by the Mental Health Research Fund. The subject selected for discussion, "Chemistry in Relation to the Development of the Nervous System," was chosen mainly because of its relevance to the causation and treatment of mental illness. Though a small meeting was originally planned the idea was found to evoke such interest that the programme had to be expanded: in addition to 12 reviews covering the main aspects of the subject, it was thought expedient to include also four films and 30 short papers on new unpublished work. Members attending included scientists from the U.S.A., Canada, Norway, Sweden, Denmark, Germany, Italy, Belgium, and the U.S.S.R., and only with great difficulty was it possible to limit to 70 the number who finally came.

The opening day, which was devoted mainly to the embryology of the brain, was marked by outstanding reviews by Dr. HORNE CRAIGIE (Toronto) on the development of the vascular patterns in the brain and by Dr. V. HAMBURGER (St. Louis) on recent advances in experimental neuro-embryology. This included an excellent account of Dr. Hamburger's own work on the development of a nervous supply to implanted tumour and other tissues. Dr. DENIS HILL (London) contributed a paper of considerable clinical interest on the changes in the E.E.G. during the maturation of the brain.

### Oxygen High in Young Brain

On the second day the main reviews by Dr. J. FOLCH (Boston) on the chemical composition of the brain during maturation, and by Dr. D. RICHTER (Cardiff) on the metabolism of the developing brain, were supplemented by a series of papers on brain biochemistry. The discussion which ensued on the lipids in the developing brain brought out important new advances that were discussed by Dr. R. W. SPERRY (New York), Professor E. KLENK (Cologne), Dr. R. M. C. DAWSON (Oxford), and Dr. FOLCH. It appeared in fact that most of the experts on the lipid metabolism of the brain were present. Dr. G. BRANTE (Eskilstuna, Sweden) also contributed to the discussion, and described the properties of a new muco-polysaccharide present in brain tissue. Dr S. S. KETY (Washington), who has succeeded in measuring the oxygen consumption of the brain in young children, reported astonishingly high values. These show that the brain may account for as much as three-quarters of the total metabolism of the resting body during the early formative years, when the basis of personality is being laid down. The oxygen consumption of the brain rises to a maximum at about the time of adolescence, and falls off later in life with advancing years. Dr. O. H. LOWRY (St. Louis) described some spectacular new work on the application of ultra-micro-methods, giving information about the localization of the biochemical changes occurring in the brain. This work has indicated that much of the metabolic activity of the brain takes place in the region of the dendrites of the nerve cells.

### Treatment of Mental Deficiency

Further sessions were held on the blood–brain barrier, which was reviewed by Dr. H. WAELSCH (New York), on brain enzymes, reviewed by Professor L. B. FLEXNER (Philadelphia), on the chemical genetics of mental illness, reviewed by Professor L. S. PENROSE (London), and on endocrine factors related to the nervous system, reviewed by Professor G. W. HARRIS (London). Dr. J. T. EAYRS (Birmingham) discussed the way in which the maturation of the brain is

affected by thyroid deficiency, and Dr. H. BICKEL (Birmingham) reported some promising new experimental work on the treatment of mentally defective children suffering from phenylketonuria. He has found that the physical and mental condition of these children can be greatly improved by putting them at an early age on a special diet low in phenylalanine. Professor J. ELKES (Birmingham) reported interesting work on the cholinesterases in the rat brain and on the effect of drugs on postnatal development. Professor R. W. GERARD (Chicago) and Sir RUDOLPH PETERS (Oxford) described new advances in our understanding of the metabolic changes in the brain associated with convulsive states.

The whole conference was characterized by the high standard of the papers and the liveliness of the discussions. It is to be hoped that the proceedings, which are to be published soon by the Academic Press Inc., will retain something of the glow of enthusiasm that marked one of the most successful conferences in this field ever held.

# Correspondence

### Scurvy

SIR,—Dr. H. R. C. Riches introduces his interesting clinical memorandum (*Journal*, July 31, p. 286) on scurvy with the statement: "Frank scurvy is now almost a clinical curiosity in this country." This may be true of England, but north of the Border we still regard scurvy as a fairly common disease.

In the nine-year period from February, 1939, to March, 1948, 58 cases of florid scurvy were admitted to the wards of one medical unit in Stobhill General Hospital, Glasgow. During this period the bed-state in the unit varied between 120 and 200. The clinical details of 40 of these cases have been checked from the case records. All but one of these patients had extensive subcutaneous haemorrhages in the legs and about 75% of them had gross anaemia. During the past six years, with a bed-state of about 120, 17 cases of scurvy have been admitted, making a total of 75 cases over a period of 15 years. All of these patients recovered.—I am, etc.,

Glasgow, W.2. STANLEY ALSTEAD.

SIR,—It was interesting to read Dr. H. R. C. Riches's account of scurvy in a patient of 56, the result of deliberate dieting (*Journal*, July 31, p. 286), but to describe the condition as a rarity or a clinical curiosity in this country is surely an overstatement. It is by no means rare amongst males of the older age group. They are usually old age pensioners with no other means, who live alone or in hostels where sleeping quarters only are provided. They fend for themselves, and inquiry reveals that they subsist on a wholly inadequate diet, chiefly of carbohydrate, have no interest in fresh fruit, and find the purchase of fresh green vegetables beyond their means.

The common misdiagnosis is thrombophlebitis, the tender induration of the calf being mistaken for thrombosis of a vein, when in fact it is a haemorrhage into the muscles or subcutaneous tissues. But it may present as haematuria, when it is passed off as bleeding from prostatic veins, the patient being a male of the appropriate age. As is often the case, the condition would probably be diagnosed more frequently if it were kept in mind, and it is wise to inquire into the dietary habits of any elderly person presenting with haemorrhage into the legs (petechiae, purpura, or ecchymosis), or brawny induration and discoloration of the lower third of the legs, hot to the touch. Confirmatory evidence is frequently lacking, as follicular hyperkeratosis may be absent and the gums not spongy or bleeding, the patient being edentulous.

When diagnosed, the response to treatment is most gratifying, and I am constantly intrigued at the rapid disappearance of induration and discoloration from around the malleoli and popliteal space when ascorbic acid is given in adequate amounts. Physiotherapy is, of course, a help, and it goes without saying that the deficiency in the other vitamins should be made good and a full and balanced diet given.—I am, etc.,

Liverpool, 8. B. K. ELLENBOGEN.

### Another Unusual Complication of Scabies

SIR,—Dr. Stephen Gold's letter (*Journal*, July 17, p. 175) reminded me of a girl seen some nine years ago in the casualty department of a children's hospital. A letter of introduction referred her as a case of chorea, and she could indeed hardly keep her arms and body still. When she had undressed, there was little doubt that she had scabies. All other findings were within normal limits.

Dr. Gold's case is a striking illustration of dangers arising from failings to which, in some degree, doctors of all ages are prone. I should like, however, to support most strongly his implied plea for seeing the somatic wood before the psychic trees. This metaphor is, however, inapt, since a somatic cause is not composed of a number of smaller psychic factors. I do not think that anything better has yet supplanted the old maxim that, whatever the patient's complaint, psychic factors should be ignored until the physical body has been thoroughly examined. If thereafter psychiatric examination indicates that the trouble is psychogenic, it will only very rarely be found that phenobarbitone, even in large doses, or antihistamines (this list could obviously be lengthened) by themselves are effective in restoring health—only in fact in those cases where the cause of the trouble is of a strictly temporary nature and especially if it is not of the patient's own making.—I am, etc.,

London, W.C.1. H. JULIE ALTSCHULOVA.

### Contamination of Injection Solutions

SIR,—Drs. J. H. Thomas and J. Marks (*Journal*, July 10, p. 87) rightly draw attention to the danger of accidental contamination of injection solutions of antibodies with organisms which are not sensitive to the particular antibiotic. There have been numerous recorded instances of infection of multi-dose containers prepared without the addition of a preservative and the consequences are particularly grave when the solution is used for more than one patient. In the course of an investigation into methods for maintaining sterility in eye drops against infection by *Ps. pyocyanea* (awaiting publication) we found that one of the most useful materials for preventing dangerous contamination of injection solutions was chlorocresol 0.1%.

In view of the increasing frequency of contamination it would appear that the addition of a preservative to the sterile water used with antibiotics is necessary.—We are, etc.,

M. KLEIN.
E. G. MILLWOOD.
W. W. WALTHER.

London, E.11.

### Blood Changes Associated with Disseminated Tuberculosis

SIR,—Dr. J. R. Fountain (*Journal*, July 10, p. 76) and Drs. Jane M. Fullerton and A. G. C. Cox (*Journal*, July 24, p. 243) have once again drawn attention to the importance of recognizing that various blood dyscrasias may be due to tuberculosis. In 1953 Lintott and I[1] reported a case of leukaemoid reaction who survived for fifteen months as a result of treatment with streptomycin and P.A.S., and five other cases of aplastic anaemia and granulocytopenia in which florid tuberculosis was found at necropsy or proved during life. We stressed the fact that tubercle formation might be absent and that all that might be found were necrotic areas in glands, liver, or spleen. Unless these were stained by the Ziehl–Neelsen technique their tuberculous nature would be overlooked. We emphasized the difficulty of diagnosis during life, but suggested, in view of the usual fatal outcome of these cases, that streptomycin and chemo-

therapy should be tried, especially where there was much fever, a family history of tuberculosis, or doubtful lung shadows. We tried liver biopsy as a diagnostic aid, but found it rather hazardous.

In February, 1954, a very ill, anaemic girl of 28 was admitted as an abdominal emergency, but laparotomy revealed nothing abnormal. Blood investigation showed haemoglobin 38%; R.B.C. 1.96 million per c.mm.; M.C.V. 80/$\mu^3$; M.C.H. 30; W.B.C., 1,000 per c.mm.; polymorphs, 60%; lymphocytes, 40%; platelets, 16,000 per c.mm.; bleeding time 15 minutes; prothrombin index 49%. Haemorrhages were present in the skin and retina. She ran a fever between 101° and 103° F. (38.3° and 39.4° C.). Blood cultures were negative. *X*-ray examination was negative. No choroidal tubercles were seen. Mantoux test positive, 1/1,000. C.S.F. normal. Marrow biopsy showed a hypoplastic marrow. The only drugs she had received were phenobarbitone, caffeine, and belladonna. It was decided that nothing could be lost by giving her streptomycin and isoniazid. Her fever began to fall three days after starting treatment and was not completely normal till five weeks later. During this time she had seven pints of blood. Her blood picture returned to normal after four weeks and has remained so. Streptomycin and isoniazid were given for four months in all. Her mother says she is now better than she has been for two years, and this suggests a gradual deterioration in her health for some time before admission to hospital.

It may be that this girl has had a spontaneous remission, and her fever may have been due to her anaemia. There is no proof either way. Because the outlook for the majority of these patients is so hopeless and the association of tuberculosis with various blood disorders so little recognized, I have felt it worth while reporting this case.—I am, etc.,

Ipswich. J. W. PAULLEY.

REFERENCE

1 *Arch. Middx. Hosp.*, 1953, 3, 161.

## Osteoarthritis and Rest

SIR,—The paper under this heading (*Journal*, July 31, p. 269) by Drs. F. Dudley Hart, Monica Watkins, Denis Burley, and M. T. Richards, written with the advice and support of Professor J. H. Kellgren, M. H. M. Harrison, and G. E. Lloyd-Roberts, is so directly opposed to the evidence I have produced over the past twenty years from personal experience and from the investigations of many hundreds of patients, and so fraught with danger to the afflicted, that I beg the use of your pages to make a strong criticism, particularly as their statements are made without the production of any original evidence.

I have demonstrated and published more recently[1 2 3] clinical and radiographic evidence which clearly proves (1) that osteoarthritis is a localized expression of a generalized condition associated with ageing; (2) that in the presence of certain metabolites trauma will initiate its development or aggravate it if it is already present: that trauma to defective joint surfaces includes that which would be considered as normal function to a mechanically sound joint; (3) that progress of the destructive process is extended and much accelerated if all restrictions due to pain are removed, as by destruction of the nerve to the joint; (4) that rest is the only factor which permits of restitution from early osteoarthritis as can be demonstrated by radiography after the opposing bony surface has been removed or after the joint has been fixed by a bridge across it; (5) that osteoarthritis without discipline as to fatigue, food, etc., brings about a vicious circle wherein rest, enforced by pain, leads to an increase in the superincumbent weight, which in turn leads to impairment in the elimination of waste products—both factors aggravating the existing degeneration; and (6) that undisciplined function of any organ showing degeneration will lead to its destruction—the more the quicker and *vice versa*.

Their statement: "Overexertion and excessive use of an affected joint will produce a sharp reaction within the next 24–48 hours, but immobility may produce a much longer disability. This is a lesson we have learned not from a study of patients in beds for rheumatic sufferers but in the general medical wards, where cardiac decompensation, bronchitis and bronchopneumonia, coronary thrombosis, bleeding peptic ulcers, and other diseases, usually in patients over 60 years of age, cause immobilization in beds for periods of several weeks" surely indicates that they have not appreciated the fact that it is not the rest but the cause for the rest which aggravates osteoarthritis. It should not be necessary for me to point out that there is a relationship between pulmonary disease (and gastro-intestinal disturbances) and bone and joint pathology, but that the acute changes brought on in the conditions cited are not degenerative conditions in the sense that true osteoarthritis is. The latter term is used all too loosely. If osteoarthritis existed previously then these conditions aggravate it; they will not produce it.

They quote opinions to the effect that the pain in osteoarthritis is due to stretching of the capsule of the joint, but they produce no original evidence to prove this. Personally, I know that this is not the explanation. As a victim of osteoarthritis for more than 20 years I know I can secure a large measure of freedom from pain by rest, I can markedly aggravate it by fatigue from any cause, and that even when resting it can be brought on with severity by anything which causes gastro-intestinal disorders or by the taking of certain vegetable laxatives; but that colonic lavage can check it.

Surely the reason why "heavy individuals suffering from degenerative joint disease are obsessed with the idea that their joints will become stiff unless they exercise them continuously" is because they have been repeatedly told this untruth by those who are ignorant of the causes. An osteoarthritic joint never ankyloses of itself by rest: if it did, this would be the pleasantest (and cheapest) method of treatment, since with sound fixation its chief feature, pain, would cease.

Their advice that "elderly osteoarthritic patients should be mobilized as soon as possible" and that "analgesics should be used freely over such active periods if pain prevents proper co-operation, for effective analgesic 'cover' for exercises is invaluable," and that phenylbutazone may bring useful relief, though they admit "it is a toxic agent which brings gastric irritation and salt retention with resulting oedema and precipitation of congestive heart failure" will indicate clearly to the doctor victim how little they understand of the condition. Why resort to such harmful measures when disciplined rest as I have publicly demonstrated is the only factor which permits of restitution and it is free from harm. The good God gave us pain to secure fixation and rest. Why abuse the gift?—I am, etc.,

Birmingham, 15. JAMES F. BRAILSFORD.

REFERENCES

1 *Brit. J. Radiol.*, 1952, 25, 76.
2 *The Radiology of Bones and Joints*, 1953, 5th ed. Churchill, London.
3 *Rheumatism*, 1954, 10, 1.

## A Thousand Families in Newcastle-upon-Tyne

SIR,—The annotation (*Journal*, July 31, p. 292) entitled "Illness in Infancy" described the medical and social survey of one thousand families in Newcastle that was planned and carried out by the late Sir James Spence and three colleagues.[1] The annotation gives the first place to a factual account of the clinical findings, and then describes the planning and purposes of the investigation, and its conduct by health visitors and a team of four medical men. This medical team consisted of Sir James Spence, Dr. Walton, M.O.H. for Newcastle-upon-Tyne, and two hospital physicians. The enterprise began in 1947, and, besides gathering many interesting clinical data, has also raised important questions of a medico-social and medico-political kind. I should like to make some brief remarks on these, for they concern the whole *political* structure of infant and child health, and of the nursing and medical services that work for it.

*Health Visitors.*—In the report great importance is attached to the work of health visitors, and a plea for their better training is made. I am specially interested in this and have recently written in support of it (*Journal*, March 6, p. 533). The Newcastle report will strengthen this young, although not new, order of British nurses, and in time they will bring it in power and popularity alongside the hospital nurses, the midwives, and the district nurses.

*The Family Doctors.*—The happiest relations have existed for years at Newcastle between general practitioners and hospital physicians; and before the investigation began its nature was explained and every effort made not to interfere with family practice. But the report, looking to the future, considers that the health visitors may become a more definite service of home and health nurses, and in their work may become more closely associated with the family doctor. If this happens it may bring many family doctors into the infant domiciliary service; and if this happens, suitable medical education in the hygiene illness of infancy and children will have to be provided for medical students.

The report is written in a stripped and bare style and with great caution and modesty in drawing conclusions. But it is unique for the refined courtesy it inculcates upon all members of the staff when they enter any home; and it shows a like sympathetic attitude in dealing with family doctors. The publication of *A Thousand Families* so soon after Spence's death seemed to give an added sting to death—this appearance of only the first instalment of an unfinished medical enterprise:

> "But the fair Guerdon when we hope to find
> And think to burst out into sudden blaze,
> Comes the blind Fury with th' abhorred shears
> And slits the thin-spun life. But not the praise."

Praise will not be lacking for this first chapter, with its store of valuable facts and its promise of things to come: and we may rely upon Spence's three colleagues to continue the work of collaboration so well begun. This experiment at Newcastle under the arresting title *A Thousand Families in Newcastle-upon-Tyne* will draw wide and close attention, and will continue to do so until it is complete.—I am, etc.,

Garvald, East Lothian. CHARLES MCNEIL.

REFERENCE

[1] *A Thousand Families in Newcastle-upon-Tyne*, 1954. London.

## Pitocin in Obstetrics

SIR,—Drs. M. Lesser and G. A. Eason (*Journal*, July 10, p. 79) reported a death following the addition of 30 units of "pitocin" to less than one litre of a glucose drip. We have used this form of therapy in many hundreds of cases of labour and never, in the first instance, add more than two units of pitocin to a litre of solution, and never deliver more than 5 milliunits of this hormone in any minute. Whatever was the cause of the reported death, the use of such large doses of pitocin will certainly cause foetal, if not maternal, death, and will bring a valuable method of treatment into disrepute.—I am, etc.,

Bradford. G. W. THEOBALD.

## Varicocele and Male Subfertility

SIR,—Animal and other experimental work upon the thermo-regulatory function of the scrotum leaves no doubt that a prolonged testicular temperature approaching that of the abdomen will depress spermatogenesis. To Dr. H. A. Davidson[1] must go the credit for applying this knowledge to a controlled clinical experiment, further results of which are in the process of publication. Various factors will raise the testicular temperature—general hyperpyrexia as in fevers, certain occupations such as stoking and foundry work, tight scrotal supports, congenitally short spermatic cords, and, of course, hydroceles and varicoceles. It is perhaps unfortunate that the last item has received attention out of proportion to its incidence. However, having excluded the more obvious causes above, we have now reached the stage where, if we have a man with a depressed sperm count but no clinical abnormality other than a varicocele, we can predict that careful excision of his varicosities is most unlikely to cause any harm, whereas it will probably improve his fertility. The problem, therefore, is not will this operation achieve the results we anticipate, but whether we should do it at all. None of your correspondents deny that it works, but they say that it should not be performed.

Since I am not acquainted personally with Dr. H. S. Russell's work I do not know how many subfertile male patients he encounters or how many he has operated upon, but he nevertheless suggests that the operation is not effective (*Journal*, July 24, p. 241). Comment from a greatly respected member of the surgical profession such as Sir Max Page (*Journal*, July 31, p. 300) has to be taken more seriously, since a chance remark from a great man can delay or accelerate progress quite considerably. Sir Max Page remembers that the removal of a varicocele 40 years ago was not always satisfactory, and it was this experience that caused his generation to teach my generation 20 years ago not to do this operation. This lesson we have faithfully followed, and I agree that a sudden fashion for the indiscriminate removal of varicoceles without proper indication would be a great pity and would not advance the cause of subfertile men. However, Sir Max Page has nothing else to offer them, whereas it is possible that this operation has. I am sure he will remember that 40 years ago his generation of clinicians also taught my generation that the male was rarely responsible for a subfertile union (unless he had suffered from a bilateral mumps or gonococcal infection). Those of us interested in this problem to-day fear that the male may be at fault in at least 50% of subfertile marriages. In short, the subfertile male was not recognized 40 or even 20 years ago, so that the present problem did not exist. It is also fair to add that the type of operation for varicocele described in a textbook of surgery 25 years ago causes me no surprise that its results were not always satisfactory.

This brings me to the brilliant work of the Liverpool anatomy school, chiefly by Professor R. G. Harrison[2] and E. W. Macmillan.[3 4 5] Here, however, clinicians must avoid placing too much reliance on pathological animal experiments when studying physiological human problems. I cannot envisage any occasion where a man would expose his testicles to −6° or −8° C., and I am not a bit surprised at the results of this procedure in the Liverpool rats. Nevertheless, if we discard this particular "red herring," this work, carefully and ingeniously devised and carried out over several years, forms a scientific background to the temperature-regulating theory. But here again, in surgical practice we should not rely too much on anatomy learned from the animal or from senile cadavers in the dissecting room, since as far as I know, varicoceles are rare in both groups. A fact which is not generally realized is that many of the large varicoceles we palpate in young men are not enclosed in what we have always called the "pampiniform plexus" at all. They are a separate set of wide, loose channels arising in a cluster round the epididymes. They are ¼ to ½ in. (3.2–6.4 mm.) in diameter and can be dissected off individually at this level.

Professor Harrison[6] has stated that the optimum site for ligature of a varicocele is high up in the cord where all the veins become merged into large channels. Unfortunately the arteries are also in large channels in the cord, and it is not until one reaches the epididymal area that the collateral circulation becomes so diffuse that the sacrifice of a few minute invisible arteries causes no harm. I have never yet seen an artery in this region, and have not yet encountered any atrophy following removal of the accessory veins at this level. The pampiniform plexus itself is not removed as Dr. H. S. Russell appears to think.

When I encounter a subfertile man who is clinically normal apart from his varicocele, particularly if he has shown some response to cold sponging, I feel that I can honestly say to him that he will be no worse off than he is, while he may be greatly improved by the operation. If such ethics were applied to surgery in general much less operating would be done.—I am, etc.,

London, W.1. HOWARD G. HANLEY.

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[1] *Proc. roy. Soc. Med.*, 1953, **46**, 841.
[2] *Fertil. and Steril.*, 1954, **5**, 205.
[3] *Proc. Soc. Fertil.*, 1952, **4**, 43.
[4] *Fertil. and Steril.*, 1953, **4**, 101.
[5] *Brit. J. Urol.*, 1954, **26**, 60.
[6] *J. Anat. (Lond.)*, 1949, **83**, 267.

## Engineering and Industrial Hygiene

SIR,—Dr. R. N. Wilson in his letter (*Journal*, July 17, p. 176) states that employers' organizations investigate health and safety in their particular industries and that some insurance companies have inspectors who visit factories and give advice. It would be interesting to know what proportion of British industry is effectively covered by such schemes, and what training is received by these inspectors.

Common-law actions are not altogether to be deprecated: they act as a spur to vigilance on the part of employers, though compensation-mindedness on either side is a bad thing.

The success of medical examinations and *x*-rays of the spine in excluding those liable to injury is, I think, very doubtful. The same of course applies to dermatitis.

The point I wished to make in my previous letter was that proper washing facilities, better factory hygiene, and skilled supervision at work could do much to prevent the occurrence of dermatitis, which constitutes the major item in claims for industrial compensation.—I am, etc.,

Farnham Royal, Bucks. M. E. M. HERFORD.

## Warmth in the Treatment of Shock

SIR,—"Shock," be it the result of body injury with or without blood loss, fatigue, emotional stress, etc., is Nature's way out of a difficulty. In all these eventualities there is a sudden and urgent call for increased supply of oxygen.

The first effect of this is on the suprarenal glands, which immediately introduce an augmented supply of adrenaline into the circulation. The result is two-fold. The first is transient and due to vasoconstriction of the peripheral circulation evidenced by the sudden pallor of the patient. The second is a little slower but much more lasting, and this is where the splenoadrenal mechanism comes into play. The stimulation of the adrenaline in the blood causes the spleen to forcibly contract and relax, and thus shoot into the general circulation armies of red blood cells, many of which are already oxygenated and the rest pick up their ammunition in passing through the lungs.

Warmth in the treatment of shock, therefore, must be quite irrational and contraindicated, as Dr. W. N. Leak points out (*Journal*, July 24, p. 240). The application of heat to the skin, by causing dilatation of the peripheral vessels, causes a rapid loss of body heat, which is the last thing we want in a patient suffering from shock. We are merely interfering with Nature.—I am, etc.,

London. D. C. MACDONALD.

## Missile Wounds

SIR,—Colonel A. J. Clyne's account (*Journal*, July 3, p. 10) of the management and fate of missile wounds in Malaya makes thrilling and heartening reading. To those of us who played some part in it, it is satisfactory to know that the use of the standard methods learnt from experience during the second world war has "served to confirm their soundness." It is even more satisfactory to read that a really alert consultant is ever on the look-out for possible advance on these standard methods: in other words, that, having grasped fully the fundamental principles underlying these methods—namely, that "environment dictates management"—he is watching for some change in his environmental circumstances that will safely permit a rather more advanced technique. I refer, of course, to the employment of primary suture, and he describes the special circumstances permitting this in Malaya—namely, minimal contamination, early evacuation to a military hospital, and the fact that casualties could be held there until convalescence was completed.

Whilst I was surgical consultant to A.A.I. in Italy during the second world war, we encountered just such circumstances during the quietude of the winter of 1944–5, the chief factor being that the administration could guarantee that patients could be held in forward hospitals for a full 10 to 14 days. With the full co-operation of the administrative staff, and fortified by the knowledge that primary suture had been successfully employed during the static phases of even the first world war,[1] it was decided to second two units for the purpose of treating specially selected cases by primary suture, the criteria for selection being that wounds should be no more than 12 hours old, and that they should be essentially superficial—that is, without nooks and crannies in the deeper parts. The results amply justified the trial. All this, in full detail, was included in one of my five extensive reports to the War Office on war surgery in Italy. But I fear that these reports have been lost since. Although I know that during the war extracts from them were sent by the consulting surgeon to the Army to all British headquarters throughout the world, no mention is made of them or their contents in the *Medical History of the Second World War*.[2] However, "an experiment in primary suture" was described in my contribution to the *British Journal of Surgery*.[3]

The important thing for Army consultants to do is what Colonel Clyne has done—namely, to keep a constant watch for any temporary improvement in environment that may justify a change in routine, and to advise accordingly. Such an assessment can only be made by a consultant who is continually moving about amongst the medical units, thus getting a living picture of such things as a temporary roadblock, with delay in evacuating urgent cases, such as major muscle wounds; overloading of one particular surgical unit; the arrival of a new, somewhat inexperienced, surgical team in forward areas; a quiet spell and an abundance of beds; a static phase and short lines of evacuation, etc.—I am, etc.,

Birmingham, 15. F. A. R. STAMMERS.

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1 *Official History of the War (1914-18), Medical Sciences: Surgery*, 1922, Vols. 1 and 2. London.
2 *Medical History of the Second World War: Surgery*, 1953. London.
3 *Brit. J. Surg.*, 1949, War Supplement No. 2, 274.


## Cystectomy in Carcinoma of the Bladder

SIR,—In the summary of my paper to the Section of Radiology at the B.M.A. Annual Meeting on carcinoma of the bladder it is stated (*Journal*, July 24, p. 234): "Out of 29 patients treated by cystectomy in the period 1949–53, 24 were alive." The number treated should read 39. I draw attention to the error as the figure quoted indicates long-term survival for a higher proportion than can be claimed. As illustrative of expectations after cystectomy the following facts relative to the patients, 9 in number, on whom I performed this operation in the year 1949 were given. One died on the third post-operative day, one in three months, one in seven months and another after three years and seven months. Five of the nine are alive and have now entered their sixth post-operative year.—I am, etc.,

Glasgow. ARTHUR JACOBS.

## General Practice in America and Great Britain

SIR,—I read with great interest the letter from Dr. D. Stark Murray (*Journal*, July 24, p. 241), concerning domiciliary visiting by pathologists. I am not certain where Dr. Stark Murray gets his facts and figures from, but I think it should be questioned that "in pathology practically all domiciliary visits are made by whole-time consultants, and that it is to them that the general practitioner in almost every area looks for his laboratory assistance." I just do not believe that this is true throughout the country, though, of course, as Dr. D. Stark Murray well knows, there are some regional hospital boards who deny pathologists the right to have a part-time contract, or to change to such a contract from a whole-time one. No doubt Dr. Stark Murray, as a former member of the South-West Regional Hospital Board, is aware of this unreasonable restriction.

In dealing with this question of domiciliary visiting by consultants, it has been mentioned many times, especially by the whole-time consultants, that general practitioners do not call them out because they know whole-time consultants do not get paid for domiciliary visits. Here we have a contrary statement by a whole-time consultant. I am sure that if Dr. Stark Murray altered his contract from a whole-time one to a part-time one he would find two

rather satisfactory results: (1) that he was, himself, called out far more than at present, and (2) that he would get paid for the domiciliary visits.

One of the most important matters, however, arising from this letter is that a large number of pathologists in several regions of the country are unable to obtain a part-time contract, as the majority of advertisements in the journals for consultant pathologist posts are for whole-time posts, with no option to choose between a part-time or whole-time contract. There are exceptions, however, one of which is the South-East Metropolitan Regional Hospital Board, who give this option, which is, I think, very much to their credit.

With the likelihood of a whole-time medical service being pressed on the profession in the future, it is in my opinion essential that *all* consultant posts in future should be advertised with an option as to whether the candidate wishes a whole-time or a part-time contract, the choice to be taken by the successful candidate on appointment. Further, I consider that consultants who have a whole-time contract, and wish to change to part-time, should be allowed to change to part-time service by agreement with their hospital board, after giving reasonable notice of their desire for such a change. The part-time consultants also should have this option to change to whole-time service if they so desire. The Central Consultants and Specialists Committee I believe are considering this matter of the option concerning change of contract, and I trust that they will press it forward to the Joint Committee.—I am, etc.,

Beckenham, Kent. JOHN KEALL.

SIR,—Dr. D. Stark Murray's statement (*Journal*, July 24, p. 241) that Scottish general practitioners do not get a laboratory service to assist them in their practice is made so emphatically that I am sure he must have carried out some preliminary investigations on the spot before writing. He must, however, as his guide in Caledonia, have used one of these maps so popular with South British advertisers which set the northern limit of this island somewhere about the Forth and Clyde canal. Had he made his way as far as the Highland capital he would have found a land where for nearly a score of years the general practitioner has been able to have carried out all reasonable pathological investigations.—I am, etc.,

Inverness. JAMES BRUCE.

## Homosexuality

SIR,—I am reluctant to ask you to continue this correspondence, but there is one final point which I feel should be noted. Dr. C. G. Learoyd in his letter (*Journal*, July 24, p. 245) states that England has an affinity with America and the Colonies inasmuch as they must all punish, with life imprisonment, homosexuality, whereas in the Continental countries it can be adequately controlled by the lenient Napoleonic Code. Surely the inescapable conclusion is that it is more rife and severe here than on the Continent. I am acquainted with the recent literature on this illness, and know nothing to support this view, but if it is so then surely the time has come when we should find out why.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

SIR,—If a bachelor indulges in homosexual practices with another man he is liable to be prosecuted as a criminal. If a married man indulges heterosexually with another woman the law takes no cognizance of it unless his wife chooses to bring a civil action against him for divorce. In the first event only two consenting adults are involved; the second concerns in addition, and unwillingly, another adult and any children of the marriage there may be.

The logic of this situation has always escaped me, and nothing that has been said in the current correspondence —least of all Dr. C. G. Learoyd's two letters (*Journal*, June 5, p. 1326, and July 24, p. 245)—has persuaded me to regard homosexuality as more evil morally or more harmful to society than adultery. It is more objectionable only because it is anomalous anatomically and physiologically. I am less concerned about the possible danger to Dr. Learoyd's "great army" of scouts, schoolboys, and students than I am about the definite psychological harm sustained by the children of parents divorced on grounds of adultery. Seduction of young people, of course, whether homo- or hetero-sexual, is a matter of which the law rightly takes a serious view, but, as regards consenting adults, it is odd that even in our profession there appear to be many who are unable to discuss homosexuality and adultery equally dispassionately.—I am, etc.,

Loughton, Essex. DONALD V. BATEMAN.

SIR,—In these days of equal pay and equal opportunity for the sexes it is strange to see male perversion condemned with such fervour by Dr. C. G. Learoyd (*Journal*, July 24, p. 245) while there is complete silence on the subject of lesbianism. One wonders if this is because there is less first-hand experience of the subject among doctors, because it is in some mysterious way harmless as compared with male perversion, or because it simply does not exist. If perversion is the crime it is held to be, then females should also be held legally responsible ("... an evil that must be firmly squashed ... there must be no sloppiness"). If it is not a crime among females then there is no reason why it should be among males.

It is to be hoped that the Royal Commission on the subject will bear this peculiar and archaic relic of sexual discrimination in mind.—I am, etc.,

Liverpool. H. E. VICKERS.

## "Sulphatriad" Anuria

SIR,—Dr. D. G. Wilson (*Journal*, July 31, p. 302) is in error in stating that the cases reported up to 1952 of haematuria and crystalluria following sulphamerazine therapy were all due to gross overdosage. I reported a case (*Journal*, October 18, 1952, p. 882) in which crystalluria causing obstruction of the urethra in a boy aged three years followed the personal administration of the drug in correct dosage, at 12-hourly intervals and with a plentiful fluid intake.

I agree that one does not now see many references to the toxicity of sulphamerazine in the medical press, but this I would attribute to the awareness of the profession of the dangers of this relatively insoluble sulphonamide, resulting in its diminishing use. Furthermore, our increasing choice of powerful antibiotics, free from risk of complications along the urinary tract, renders the sulphonamides as a group less the drugs of election, particularly in general practice.

Dr. Wilson has been fortunate in avoiding the urinary complications of sulphamerazine therapy, but the solubility of the drug has not altered since 1952. Even if such complications were due alone to overdosage (and we cannot guarantee that our directions will be followed unerringly), surely it would be wiser to prescribe the safer, more soluble sulphonamides, which will produce the same clinical result with less risk of urinary tract disaster if overdosage should occur accidentally. I feel that one case only of crystalluria in his practice would be sufficient to alter Dr. Wilson's opinion, and it is evident from his reference to the law of averages catching up with him that he has some uneasiness in the matter. It is, I submit, preferable to burden the "already harassed mother" with an extra dose or two of medicine to administer each day than to risk her distraction should urinary complications appear. There is nothing spectral about urinary obstruction when it happens.—I am, etc.,

Huddersfield. LESLIE BALLON.

SIR,—Dr. D. G. Wilson (*Journal*, July 31, p. 302) is on thin ice when he states that he will continue to use sulphamerazine despite the warnings published from time to time in your pages. I was careful to indicate in my letter (*Journal*, July 10, p. 102) that the anuria occurred after normal doses of "sulphatriad." After I had written my letter, but before it was published, another by Dr. Alan P. Grant appeared in the *Journal* (July 3, p. 47) pointing out the danger of using "sulpenin," which also contains sulpha-

merazine. Since then I have had a letter from a doctor in Ireland who says: "About fifteen months ago I was treating a little girl of about 3 years for measles. She started an otitis media and I prescribed 'sulphatriad' suspension 0.5 g. six-hourly—that is, considerably less than the suggested dose as it appears in the literature. The parents are very sensible, and I know that they were most careful about pushing fluids. After only four doses she developed complete anuria."

Another doctor has written to me and quoted Allen,[1] who suggests that the haematuria may be an allergic phenomenon and that the danger of using three sulphonamides arises through the increased chance of allergic response. In my cases crystals of sulphonamide were found in the urine and recovery was rapid, which suggests that the cause was mechanical and not allergic. Whatever the mechanism responsible, it seems to me to be important to record these cases as a warning to such people as Dr. Wilson, who have not yet met with similar reactions, and also to the manufacturers (who have so far made no move in the matter).—I am, etc.,

Bath. H. R. E. Wallis.

References

[1] *The Kidney*, 1952. Churchill.

Sir,—We are grateful to Dr. H. R. E. Wallis (*Journal*, July 10, p. 102) for drawing attention to two cases of severe haematuria and anuria occurring after the administration of normal doses of "sulphatriad." We hope that this correspondence will stimulate any other doctor who has had similar experiences to write to us giving fullest possible information. During the seven years which have elapsed since the introduction of sulphatriad we have received very few reports of such happenings, and in some of these there was evidence of high dosage or failure to ensure an adequate fluid intake. We have never claimed complete avoidance of this complication of sulphonamide therapy and we doubt whether such a claim could be sustained for any of the commonly used systemically active sulphonamides.

The reported incidence of these reactions with sulphatriad has been so small as to justify the statement that it is markedly lower than when the individual components are used alone in the usual dosages; we do not believe that it justifies the drastic action suggested by your correspondent or his analogy with calomel-containing teething powders. Should further evidence indicate that we have underestimated the risk of this unfortunate complication we will assuredly consider the reformulation of our product.—I am, etc.,

Dagenham. D. G. Ardley,
Medical Information Division, Pharmaceutical Specialties (May and Baker) Limited.

## Intra-arterial Therapy in Occlusive Vascular Disease

Sir,—In the article by Mr. J. Woodrow Betts (*Journal*, June 12, p. 1360) the opinion was expressed that in intermittent claudication the intra-arterial administration of vasodilators was not warrantable, whilst in ischaemic necrosis it was a valuable adjunct to local treatment. In a series of some 35 cases comprising different forms of occlusive vascular disease I have had difficulty in coming to a conclusion as to which form benefited most from intra-arterial injections, as good results were obtained equally in cases of intermittent claudication and in patients with ischaemic lesions. It is to be realized that improvement may not meet all the criteria of clinical evaluation at the same time, in the same case. Thus, in one patient the extremities may feel warmer, yet peripheral pulses may remain absent; or, ischaemic ulcers may not improve, yet the patient may walk longer distances before pain is manifest. Contrary to that of Mr. Woodrow Betts, my experience has been that intermittent claudication benefits from intra-arterial injection, and I agree with his general view that this route has opened new possibilities in the treatment of peripheral vascular disease.

Regarding substances used for injection, papaverin and tolazoline ("priscol") seem to be the most popular. I should like to endorse the statement of your correspondent, Dr. H. A. W. Forbes (*Journal*, July 17, p. 172) that tolazoline gives good results in intermittent claudication. Besides these drugs, I have, for some time now, been using a mixture of procaine amide hydrochloride ("pronestyl"), and nicotinic acid, and I must say that I have been impressed by the results, both in cases of ischaemic lesions and of intermittent claudication. In one particular patient who received more than 100 of these injections at the same site, no untoward signs were noted. Recently in two cases of threatened gangrene $\beta$-pyridil carbinol ("ronicol") was used with encouraging results.

From the appreciation of different workers who have used this route, and from my experience, I believe that percutaneous intra-arterial injection of vasodilators is a valuable procedure in the treatment of peripheral vascular disease. It presents an easy therapeutic possibility in cases where surgery is contraindicated or refused, and it successfully potentiates sympathectomy pre- and post-operatively. It is certainly worthy of wider recognition.—I am, etc.,

Huddersfield. S. A. Gueukdjian.

## Fatal Pyrimethamine Poisoning

Sir,—Dr. R. Y. Taylor (*Journal*, August 1, 1953, p. 285) and Dr. H. L. Peake (*Journal*, July 3, p. 48) have each reported a case in which an inadvertent large overdose of pyrimethamine had a fatal outcome, and in which convulsions were prominent symptoms. In experimental studies with pyrimethamine and some of its congeners, in which large doses of the drug were given to dogs and monkeys, it was observed that the convulsant activity could be prevented by the administration of barbiturates. This resulted in a significant lowering of the acute toxicity and allowed the study of the delayed effects of doses which would have been immediately lethal (due to convulsant activity) if administered alone. These observations will be mentioned, incidental to studies primarily concerned with haematopoietic effects, in a paper by L. G. Hamilton *et al.*, to appear in *Blood*.

One would suggest that the treatment of acute pyrimethamine intoxication should include the administration of barbiturates to alleviate early convulsant activity and of "leucovorin" (citrovorum factor) or folic acid and ascorbic acid to reverse the later effects on the haematopoietic mechanisms.—I am, etc.,

Tuckahoe 7, New York. G. H. Hitchings.

## Proposed Coat of Arms for B.M.A.

Sir,—I am certain that you have no inclination to have your *Journal* involved in a heraldic brawl, but as one who sent (*Journal*, July 10, p. 102) a criticism of Dr. S. F. Logan Dahne's explanation of the proposed coat of arms for the B.M.A. (*Journal*, June 26, p. 1491) I must believe that I am probably intended to be included in Dr. J. S. Hawes's embrace (*Journal*, July 24, p. 247) as one of those accused of trying to air knowledge and "having a slight acquaintance with heraldry." I have, sir, more than a slight acquaintance with heraldry and I challenge Dr. Hawes to find a single error in my letter. I believe the airing of knowledge to be a main function of any scientific journal. I must ask Dr. Hawes to exclude me in future, if he would, from his genial circle of heraldic morons.

In your next issue (*Journal*, July 31, p. 304), Dr. G. A. Macdonald tells me that I should "surely know . . ." If he would do me the honour of reading carefully, very carefully, my letter he will find that I stated there that the gold lion or leopard [alias lion guardant] passant were and are borne by a great many families and are not, either, "Her Majesty's personal property." If he should really disagree with this statement may I refer him to the coats of a few families (Engham of Kent, Ermine of Lincolnshire, Mepertishall, and Rolleston), all of which were bearing, more than three hundred years ago, a gold lion passant guardant on a chief gules?—I am, etc.,

Ipswich. Edward Elmhirst.

# Obituary

## G. W. KOSMAK, M.D., Hon. F.R.C.O.G.

Dr. George William Kosmak, for many years editor of the *American Journal of Obstetrics and Gynecology*, and a leading American gynaecologist, died at his home in New York on July 10, 14 days before his eighty-first birthday. He graduated M.D. at the College of Physicians and Surgeons, Columbia University, in 1899, and began his brilliant career in the specialty of his choice. In 1924 he was appointed attending surgeon to the New York Lying-in-Hospital, a post he held for 22 years. For many years treasurer of the American Gynecological Society, he was its president in 1944. He was a member of the committee of the New York Academy of Medicine which published an important analysis of the causes of puerperal mortality in 1930. Kosmak was at first an outspoken opponent of the birth control movement; later he was said not to have opposed contraception as such but to have preferred leaving decisions to the family physician. He also led a campaign to license and supervise midwives. His great reputation as an expert in gynaecology, both as a practitioner and as an editor, was well known to gynaecologists in this country, many of whom he welcomed to his home in New York. The Royal College of Obstetricians and Gynaecologists recognized Kosmak's eminence in his chosen field when, in 1950, he was elected an honorary Fellow of the College.

Kosmak's greatest contribution to medicine was probably as an editor. For some years he edited the *New York State Journal of Medicine*. He became associate editor of the *American Journal of Obstetrics and Diseases of Women* in 1906, taking over the full editorship two years later. When that journal ceased publication in 1919 efforts were made to replace it, resulting in the birth in 1920 of the *American Journal of Obstetrics and Gynecology*. Kosmak was the obvious choice as editor, a post which he filled with distinction until 1952, when he retired and was made advisory editor. During his occupation of the editorial chair he nursed the journal from modest beginnings to its present position as one of the most distinguished of the specialist medical periodicals. The July, 1954, issue is a *Festschrift* in his honour, containing upwards of fifty papers from all parts of the world, providing a panorama of modern obstetrics and gynaecology. It is greatly to be regretted that his death followed within a few days of the publication of this tribute.

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Dr. A. R. WALTERS died on June 26 at the age of 86 after a trying illness, for him mercifully clouded by the effects of age. Alexander Radclyffe Walters was born at Reigate, Surrey, on December 1, 1867, the son of Dr. John Walters, a general practitioner, and he always regarded his future as lying in the partnership to which his father belonged, and which had existed as a practice since 1812. He was a student at the London Hospital, from which he qualified L.S.A. in 1891, taking the M.R.C.S., L.R.C.P. diplomas in the following year. At "The London" he was house-physician, receiving-room officer, and clinical assistant in the ophthalmic department before joining the family practice in 1892. Dr. L. DULAKE writes: "Alec," as he was affectionately known to all his colleagues, was tough and industrious. Because of the absence of ancillary aids and organized services he was self-reliant from the start. In his younger days horse transport was the only means of progression over distances of any extent, and he became an expert horseman, visiting his patients either by dogcart or on horseback. He was a keen sportsman, riding to hounds and shooting and fishing when he could get the opportunity. His father had started and founded the Reigate and Redhill Cottage Hospital, the second cottage hospital in Great Britain, and Alec was largely responsible for its development into a general hospital, now the East Surrey Hospital. Another activity to which he devoted much energy was the Surrey Benevolent Medical Society. A keen member of the British Medical Association for nearly 40 years, he was chairman of the Reigate Division from 1913 to 1915 and president of the Surrey Branch from 1915 to 1919. Later in life he became a justice of the peace. Throughout his whole career he was not only a general practitioner of indefatigable energy and a competent general surgeon, but he lived a very full life and took part in all the social activities of the neighbourhood. Deeply grieved by the loss of his daughter in 1925, he never really recovered from the blow. He retired in 1931, but continued to live at Reigate, where by reminiscence and anecdote he kept alive much of the tradition and colour of medicine as practised in freer, and tougher, days. He is survived by his widow and only son, a solicitor, to whom his colleagues extend every sympathy.

Dr. M. J. MARREN died at Epsom, Surrey, on July 7 at the age of 56. Michael Joseph Marren was born in the Charlestown district of Co. Mayo on June 4, 1898, and was educated at St. Nathy's College, Ballaghaderreen, Co. Roscommon, where he excelled in both academic and athletic pursuits. He won an entrance scholarship to University College, Galway, and studied medicine there and at Dublin, graduating M.B., B.Ch. from the National University of Ireland in 1922. After working for a period as a ship surgeon he settled in practice at Epsom. J. C. writes: Joe Marren was a sincere and steadfast man who always thought before he spoke. Thus, while he did not open his heart to all, he retained an undemonstrative loyalty to the friends of his early days in particular, and few men can have had more friends. He was the founder and chairman of the Epsom Irish Association, and through his untiring work he has left behind him a well-organized and prosperous Irish club. He is survived by his widow and by brothers and a sister, to all of whom our sympathy is extended.

Dr. J. G. MITCHELL died at his home at Hednesford, Staffordshire, on July 30 at the age of 64. James Garfield Mitchell, who was born in New Zealand on June 23, 1890, was a medical student at the Otago Medical School, graduating M.B., Ch.B. from the University of New Zealand in 1913. He then held house appointments at the Otago Hospital until the outbreak of the first world war in 1914, when he enlisted as a medical officer in the first New Zealand contingent. He served throughout the war, in Gallipoli, France, and Egypt, ending up as a lieutenant-colonel in command of a field ambulance in France. After the war he came to this country and married Miss A. Norman-Smith, of Margate. He settled in practice at Hednesford in 1922.

Dr. S. C. DYKE writes: It did not take Dr. J. G. Mitchell very long to become a respected and well-loved figure in Hednesford and district. He took a very large part in establishing the Hednesford Mines Rescue Station, where he worked with the late Mr. Joshua Payton, and the work of the staff in training rescue teams achieved a national reputation. For many years he was also surgeon to the Hednesford police. During the last war he organized a mobile first-aid unit and trained the personnel. The death of his wife in 1948 was a very great blow to him, but, despite the bereavement and the fact that for some years past his health had been deteriorating, he struggled to remain engaged in his practice almost to the end of his life. He is survived by two married daughters.

By the sudden death of Dr. LAWRENCE CROMBIE on July 19 Clydebank and district has lost its oldest-established general practitioner. Born on February 7, 1889, Lawrence Crombie studied medicine at Glasgow University, where he graduated

M.B., Ch.B. in 1913. He served in the R.A.M.C. for the duration of the first world war, and thereafter settled in general practice as a junior with the late Dr. John Gilmour, who later became a pioneer regional medical officer under the old Scottish Board of Health; Crombie took over the practice, which was an old and well-established one. In 1925 he was joined as a partner by the late Dr. John E. Jeffrey (whose obituary was printed in the *Journal* of March 20, 1954, p. 709), and they formed an ideal team till about a year ago, when Crombie gave up the general practice side, retaining only his work as appointed factory surgeon for his busy industrial area. Bringing to bear a keen sense of humour, devotion to duty, and a great capacity for work, and a personality that readily obtained the confidence of his patients, he was a popular, respected, and trusted general practitioner. Crombie had a very testing double family bereavement in his middle thirties, when he lost his wife and youngest son within a few days of each other—his wife from pneumonia and the boy from a streptococcal throat infection just before the antibiotic era had dawned. In the Clydeside air raids of 1941 his house was completely burned out with the loss of all his "lares" and "penates." Such tragedies would have daunted many a lesser man, but, though scarred and bruised, he accepted his lot with Christian fortitude and held to his course. Once established in practice he took his full share in local medico-political affairs, serving on the Clydebank burgh panel committee (with a period as its chairman) and as a member of the burgh insurance committee. From the beginning of the National Health Service in 1948 he had been a member of the county executive council and of the local medical committee, being chairman of the latter for about four years up to the time of his death. Through this work his colleagues soon learned that he had a logical and incisive mind and a keen sense of justice, with ample humour to leaven the dullness of routine business. His term as chairman of the Dunbartonshire Division of the British Medical Association lasted from 1946 to 1951, when his services were acknowledged by his fellow members in a suitable presentation. His favourite pastimes were golf, angling, and his garden, and it was a blow when coronary insufficiency forced him to give up golf and active gardening some few years ago. To his recreations he brought the same vigour and enthusiasm as he did to his work. His death occurred from a severe coronary thrombosis while he was actually in the process of landing a fine salmon at Brora, in Sutherlandshire. The large and representative gathering at the funeral bore testimony to the respect in which his memory is held by the profession and the general public. He is survived by his second wife, one son, and one daughter, to whom our sympathy goes out.—I. C. A. and W. G.

Dr. G. D. LAING died on August 1 in Oxted and Limpsfield Hospital, in the founding of which he took an active part. He was 77 years of age. George Davison Laing was born at Bamburgh, Northumberland, on July 5, 1877, and received his medical education at Edinburgh University, where he graduated M.B., Ch.B., in 1899. During the South African War he served first as a trooper and later as a civil surgeon in the South African Field Force, and was mentioned in dispatches. After the war he held an appointment as surgeon captain in the South African Constabulary for a time, and later became senior assistant medical officer at Pretoria Civil Hospital. He returned to England in 1906, when he obtained the degree of M.D. (with commendation), and in the following year he married Miss Dorothy Barry. After practising for a few years at Husbands Bosworth, in Leicestershire, he settled in 1912 at Brambletye, near Limpsfield, in Surrey, and was in general practice there until he retired in 1947. During the first world war he served in the R.A.M.C. in France and was twice mentioned in dispatches. Besides being a wise, competent, and much-loved doctor, he was a man of wide interests and many activities. In his early days he represented his university at tennis and boxing, and Scotland in athletics (long jump). His sporting enthusiasm continued to the end, whether in tennis, hunting, shooting, or golf, and he was the first president of the Limpsfield Blues Football Club. Another of his interests was the Edenbridge and Oxted Agricultural Show Society, having been its president in 1947 and a frequent competitor in the hunter class. He also helped to found the Old Surrey and Burstow Pony Club and was its president until his death. For many years he was people's warden of St. Peter's Church, Limpsfield. A keen member of the British Medical Association and a staunch supporter of the Reigate Division, he was chairman of the Division from 1927 to 1929 and president of the Surrey Branch in 1945. Besides taking an active part in the founding of the Oxted and Limpsfield Cottage Hospital, of which he was at one time vice-chairman of the board of management, he was a founder member of the Rotary Club and a keen freemason, and he helped to found the Limpsfield branch of the British Legion, of which he was chairman for many years. In later life he devoted himself to the welfare of old people and was chairman of the local old people's welfare service. He is survived by his widow and three sons (two of whom are doctors) and two daughters.—C. G. W. and J. H. L.

# Medico-Legal

## INTERSEX AND MARRIAGE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Early this year[1] some of the legal implications of "sex changes" were considered in these columns. The sort of difficulties which can arise out of the marriage of intersex individuals was strikingly illustrated in the recent case of *B.* v. *B.*,[2] decided in the Probate, Divorce, and Admiralty Division of the High Court on May 11 and 12, in which a husband petitioned for the annulment of his marriage on the ground of his wife's incapacity to consummate it.

The wife had had certain male sexual organs removed by operation at the age of 17. She had no vagina and no menstrual periods, but in February, 1949, she went through a ceremony of marriage. Attempts by the husband to effect penetration in the two following months were naturally entirely unsuccessful. In March, 1949, the wife went into hospital and underwent an operation for the construction of an artificial vagina 4–6 in. (10–15 cm.) long, the mould being finally replaced by operation in July of that year. In September the husband, who had been abroad on duty, returned to England, and between then and the following April he made frequent attempts to effect penetration but with very little success, and at some stage considerable closure of the artificial vagina took place. In April, 1952, the husband left the wife, and they never lived together again.

The question for the court was whether the marriage had been consummated and what in law amounts to consummation. The commissioner in his judgment quoted from the leading decision of the Ecclesiastical Court in 1845,[3] in which the question of what amounts to sexual intercourse as a matter of law was canvassed in the context of malformation in the sexual organs of the wife which allowed of only partial connexion. In that case Dr. Lushington had decided that even though the malformation in the wife was such as to render impregnation impossible, nevertheless provided that it allowed natural coitus, as opposed to "an incipient, imperfect and unnatural coitus," the marriage could not be pronounced void. This decision was approved and applied by the House of Lords[4] in 1947 in holding that a husband was not entitled to a decree of nullity for non-consummation on the ground that his wife would not have intercourse with him without the intervention of artificial methods of contraception.

Applying the principle stated by Dr. Lushington, the commissioner held that nothing which could be said to be

[1] *British Medical Journal*, 1954, **1**, 710.
[2] [1954] 3 *Weekly Law Reports*, 237.
[3] *D.* v. *A.*, 1 *Rob. Ecc.* 279.
[4] *Baxter* v. *Baxter*, [1948] A.C. 274.

proper coitus could ever take place or have taken place between the husband and wife in the case before him, by reason of the fact that the wife's vagina was not a natural but an artificial organ, and he further decided that for the same reason the situation was incurable from the point of view of making her in the real sense capable of having sexual relations with her husband.

There are perhaps logical difficulties in reconciling this decision with the decision of the House of Lords in *Baxter* v. *Baxter*. It is certainly arguable that, if coitus in which the possibility of impregnation is excluded by artificial means can be "natural coitus," coitus in which the wife's vagina is an artificial substitute for an absent organ could equally be "natural coitus," though the possibility of impregnation is equally excluded. The truth is that the law of marriage founds on the assumption that the husband is a man and the wife is a woman. When it has to be applied to situations in which one party to the marriage is an intersex it can only do its best. It is, however, important that it should be realized that the legal difficulties which inevitably arise in the marriage of intersex individuals of the type involved in the case of *B.* v. *B.* cannot be cured by the surgeon's help, whatever he may be able to do for the individual's health.

# Vital Statistics

### Infectious Diseases

Infectious diseases were less prevalent in England and Wales during the week ending July 24. The largest declines in the number of notifications were 205 for whooping-cough, from 2,235 to 2,030, 108 for measles, from 3,073 to 2,965, and 74 for dysentery, from 608 to 534.

The largest variations in the local trends of measles were rises of 58 in Lancashire, from 604 to 662, 56 in Cheshire, from 339 to 395, and 46 in Essex, from 96 to 142, and falls of 45 in Surrey, from 83 to 38, 43 in Yorkshire West Riding, from 193 to 150, and 41 in Norfolk, from 138 to 97. 785 cases of scarlet fever, 17 fewer than in the preceding week, were notified, and there were no large fluctuations in the local trends. The largest variations in the returns of whooping-cough were a rise of 46 in Devonshire, from 23 to 69, and a fall of 37 in Staffordshire, from 78 to 41. 13 cases of diphtheria were notified, and these were 2 more than in the preceding week.

91 cases of acute poliomyelitis were notified. These were 14 more for paralytic and 14 more for non-paralytic cases than in the preceding week. The largest returns were Durham 8, Northumberland 7 (Whitley Bay M.B. 2), Cheshire 6 (Birkenhead C.B. 3, Wallasey C.B. 3), Lancashire 6 (Manchester C.B. 2, Eccles M.B. 2), Kent 5 (Margate M.B. 2), Sussex 5 (Shoreham-by-Sea U.D. 2), Wiltshire 5 (Swindon M.B. 4), Dorset 5 (Dorchester M.B. 3), Devonshire 5 (Exeter C.B. 2, Plymouth C.B. 2), and Staffordshire 5 (Walsall C.B. 4).

The largest centres of dysentery were London 96 (Fulham 21, Islington 12), Lancashire 89 (Liverpool C.B. 22, Manchester C.B. 12), Yorkshire West Riding 63 (Sheffield C.B. 32), Kent 40 (Penge U.D. 35), Leicestershire 24 (Leicester C.B. 15), Middlesex 24, Lincolnshire 22 (Boston M.B. 16), Gloucestershire 21 (Bristol C.B. 17), and Durham 20.

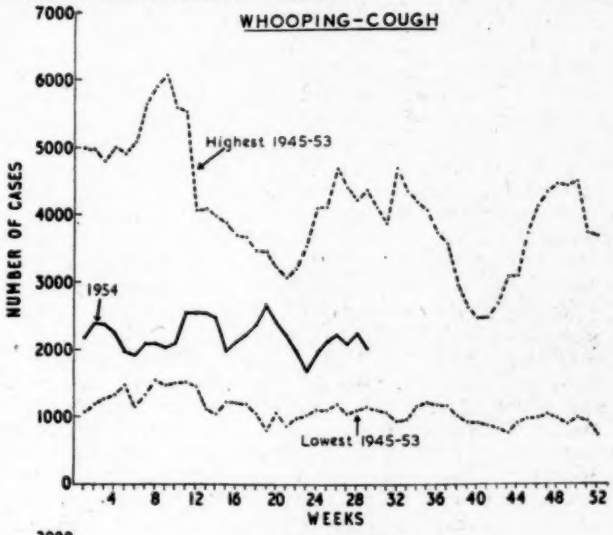
In Scotland 210 cases of dysentery were notified, being 68 more than in the preceding week. The largest returns were Glasgow 127, Edinburgh 23, Stirling county 17, and Fife county 101.

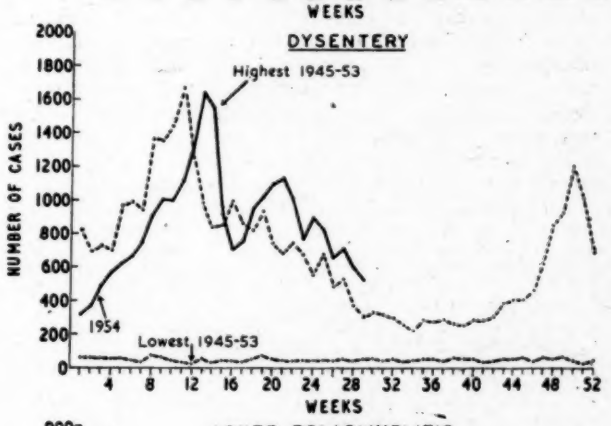
### Week Ending July 31

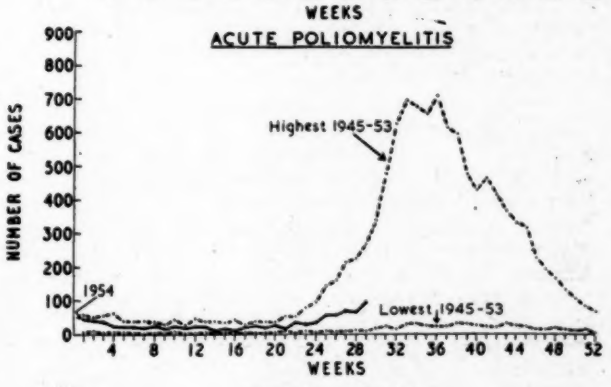
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 712, whooping-cough 2,000, diphtheria 14, measles 3,387, acute pneumonia 262, acute poliomyelitis 94, dysentery 445, paratyphoid fever 8, and typhoid fever 3.

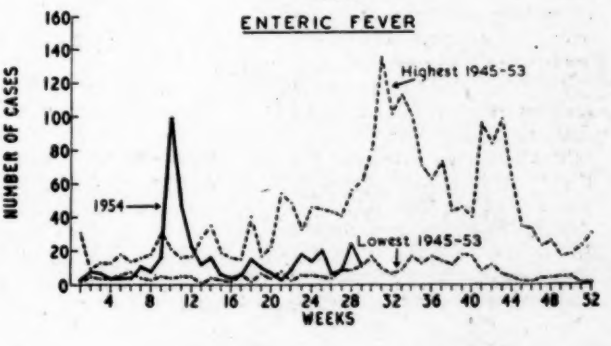
### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 24** (No. 29) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

| CASES in Countries and London | 1954 | | | | | 1953 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria | 13 | 1 | 8 | 0 | 0 | 14 | 1 | 7 | 0 | 1 |
| Dysentery | 534 | 96 | 210 | 8 | 1 | 476 | 85 | 146 | 4 | |
| Encephalitis, acute | 7 | 2 | 0 | 0 | | 8 | 1 | 0 | 0 | |
| Enteric fever: | | | | | | | | | | |
| Typhoid | 3 | 2 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | |
| Paratyphoid | 9 | 0 | 0 | 0 | 0 | 3 | 0 | 1 (B) | 0 | |
| Food-poisoning | 221 | 22 | | 15 | 0 | 475 | 40 | | 42 | |
| Infective enteritis or diarrhoea under 2 years | | | | 18 | 15 | | | | 15 | 36 |
| Measles* | 2,965 | 169 | 62 | 110 | 144 | 6,610 | 145 | 202 | 153 | 198 |
| Meningococcal infection | 31 | 3 | 14 | 1 | 0 | 47 | 1 | 17 | 1 | 4 |
| Ophthalmia neonatorum | 22 | 3 | 14 | 0 | | 37 | 5 | 8 | 0 | |
| Pneumonia† | 254 | 15 | 108 | 2 | 2 | 329 | 15 | 138 | 3 | |
| Poliomyelitis, acute: | | | | | | | | | | |
| Paralytic | 56 | 1 | 20 | 2 | 2 | 85 | 5 | 1 | 7 | 4 |
| Non-paralytic | 35 | 3 | | | | 41 | 1 | | | |
| Puerperal fever§ | 245 | 48 | 17 | 1 | 0 | 261 | 38 | 19 | 0 | |
| Scarlet fever | 785 | 45 | 78 | 18 | 17 | 1,066 | 55 | 150 | 29 | 65 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory | 781 | 77 | 133 | 39 | | | | 130 | 30 | |
| Non-respiratory | 104 | 4 | 14 | 3 | | | | 15 | 1 | |
| Whooping-cough | 2,030 | 112 | 155 | 22 | 18 | 4,690 | 355 | 370 | 42 | 41 |

| DEATHS in Great Towns | 1954 | | | | | 1953 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 |
| Dysentery | 0 | 0 | | 0 | | 0 | 0 | | | |
| Encephalitis, acute | | 0 | | | 0 | | 0 | | | 0 |
| Enteric fever | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | | |
| Infective enteritis or diarrhoea under 2 years | 3 | 0 | 0 | 0 | 0 | 9 | 1 | 0 | 1 | 0 |
| Influenza | 5 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Measles | | 0 | 0 | 0 | 0 | | 1 | 0 | | 0 |
| Meningococcal infection | | 0 | 1 | | | | 0 | 1 | | |
| Pneumonia | 133 | 24 | 16 | 5 | 4 | 131 | 21 | 15 | 7 | 6 |
| Poliomyelitis, acute | 1 | 0 | | | 0 | 8 | 2 | | | 0 |
| Scarlet fever | | 0 | 0 | 0 | 0 | | 0 | 0 | | 0 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory | 59 | 6 | 10 | 1 | 2 | 80 | 10 | 9 | 1 | 3 |
| Non-respiratory | | 3 | 11 | 0 | 1 | | 0 | 4 | 0 | 2 |
| Whooping-cough | 1 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| Deaths 0–1 year | 183 | 14 | 25 | 6 | 7 | 233 | 24 | 22 | 10 | 11 |
| Deaths (excluding stillbirths) | 4,396 | 650 | 569 | 83 | 146 | 4,196 | 606 | 463 | 76 | 153 |
| LIVE BIRTHS | 7,420 | 1080 | 970 | 218 | 400 | 8,038 | 1176 | 943 | 218 | 418 |
| STILLBIRTHS | 175 | 23 | 27 | | | 168 | 20 | 23 | | |

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Medical News

**Trilene Analgesia in Midwifery.**—The Minister of Health announced on July 30 that midwives will soon be able to administer "trilene" with approved inhalers as an analgesic in childbirth, and the Central Midwives Board has accepted a recommendation to this effect by a committee of the Medical Research Council. It will be some time before approved machines become available for use by midwives, because each machine has to be specially tested to ensure that it conforms to specification. The M.R.C. committee has been testing various methods of anaesthesia, and its report will be published in the autumn.

**Society for General Microbiology.**—This society was founded in 1945, and since 1947 has published through the Cambridge University Press the *Journal of General Microbiology* and a series of symposia. It has approximately 1,260 members and has now established a permanent office at the Institute of Biology, Tavistock House South, Tavistock Square, London, W.C.1. Applications for membership and payment of subscriptions should in future be made to this office. The meetings secretary is Dr. E. F. GALE, department of biochemistry, Cambridge University. The duties of general secretary have now been taken over by Professor K. E. COOPER, department of preventive medicine, Bristol University, who succeeds Dr. J. G. DAVIS. Newly elected members of committee are Dr. B. W. LACEY, Miss JUNE LASCELLES, and Dr. P. TATE. The president, Mr. H. J. BUNKER, the treasurer, Professor R. LOVELL, and the two editors of the journal, Professor B. C. J. G. KNIGHT and Mr. A. F. B. STANDFAST, are the other officers of the Society. The nineteenth general meeting is to be held at Reading University on September 14–16, and is to include a discussion meeting on "Principles of Microbial Classification."

**Dr. T. J. Honeyman** has been appointed a member of the Independent Television Authority and is to make the interests of Scotland his special care. Dr. Honeyman is Director of the Glasgow Art Gallery and Rector of Glasgow University, where he graduated in medicine in 1916. Many members of the B.M.A. who attended the Annual Meeting last month will remember with pleasure the reception at the Glasgow Art Gallery and the demonstration given by Dr. Honeyman and his staff.

**Chair of Physiology at Capetown.**—Dr. ARCHIBALD WALKER SLOAN, senior lecturer in physiology at Glasgow University since 1951, has been appointed professor of physiology in the University of Capetown, in succession to Professor J. T. IRVING. Dr. Sloan, who is 37 years of age, graduated M.B., Ch.B. at Glasgow in 1940. He was admitted F.R.F.P.S. in 1947 and M.R.C.P. in the following year.

**The Lister Medal.**—The Lister Medal, awarded for distinguished contributions to surgical science by a committee representative of the Royal Society, the Royal College of Surgeons of England, the Royal College of Surgeons in Ireland, the University of Edinburgh, and the University of Glasgow, has this year been granted to Mr. VICTOR EWINGS NEGUS, consulting surgeon to the ear, nose, and throat department of King's College Hospital. This award is in recognition of Mr. Negus's services to the advancement of knowledge in the surgery of the nose and throat by means of his researches into the comparative anatomy and physiology of the larynx and paranasal sinuses. Mr. Negus will deliver the Lister Memorial Lecture in London on April 5, 1955, under the auspices of the Royal College of Surgeons of England.

**Study in U.S.A.**—A hundred European doctors are to be awarded postgraduate training fellowships in the U.S.A. by the United States Foreign Operations Administration. They will undertake research in laboratories and hospitals. Fellowships will also be provided for more experienced specialists who may require brief study of particular developments.

## COMING EVENTS

**The British Association.**—The annual meeting of the British Association for the Advancement of Science is being held this year at Oxford from September 1 to 8. Dr. E. D. ADRIAN, O.M., P.R.S., has entitled his presidential address "Science and Human Nature": it is to be broadcast on the Home Service at 9.15 p.m. on September 1. There will be about 300 speakers at the meetings of 13 sections, and, as usual, many excursions and visits to places of interest have been arranged. Among the subjects of medical interest to be discussed at the section meetings are genetics and medicine (zoology), medical geography (geography), obesity (physiology), relief of pain (physiology), and hallucinations (psychology). Application for membership tickets should be made to the Secretary, British Association for the Advancement of Science, Burlington House, London, W.1.

**Tuberculosis Refresher Course** on "Case Finding and its Implications" at Bristol, September 27 to October 1. Details from Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W.C.1.

**Medical Photography.**—Fifth annual conference of Medical Group of Institute of British Photographers, September 23–26, at Royal College of Surgeons and Institute of Neurology. Open to all interested. Details from Mr. N. K. Harrison, Department of Medical Photography, St. Bartholomew's Hospital, London, E.C.1.

## NEW ISSUES

**British Journal of Ophthalmology.**—The new issue (Vol. 38, No. 8) is now available. The contents include:

OCULAR HISTOLOGY IN PREMATURE INFANTS WITH REFERENCE TO RETROLENTAL FIBROPLASIA. B. A. Ward.
POLYSACCHARIDE GRANULES IN ASSOCIATION WITH DEVELOPING RETINAL VESSELS AND WITH RETROLENTAL FIBROPLASIA. Geoffrey Serpell.
VASCULARIZATION OF THE OPTIC PATHWAY: I. LAMINA CRIBROSA AND OPTIC NERVE. J. François and A. Neetens.
EXPERIMENTAL TOXOPLASMOSIS OF THE UVEAL TRACT. J. K. A. Beverley, C. P. Beattie, and B. A. Fry.
EXTRACONJUNCTIVAL APPROACH TO THE EXTRA-OCULAR MUSCLES. M. Sarwar.
EFFECT OF RAISED OCULAR TENSION ON THE EPISCLERAL VESSELS: DEVELOPMENT OF THE CAPUT MEDUSAE IN PRIMARY GLAUCOMA. J. H. Dobree.
HYPERTROPIA CORRECTED BY CHANGES OF THE LATERAL RECTUS INSERTION. John Foster and E. C. Pemberton.
LOCALIZED INTRA-ORBITAL AMYLOID DISEASE. Ahmed Handousa.

Issued monthly; annual subscription £4 4s.; single copy 8s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

**British Journal of Preventive and Social Medicine.**—The new issue (Vol. 8, No. 3) is now available. The contents include:

A STUDY OF TWO YEARS' WORK IN NORTHERN IRELAND GENERAL PRACTICE. J. C. C. Crawford.
RECENT TRENDS IN SURVIVAL OF PATIENTS WITH RESPIRATORY TUBERCULOSIS. C. R. Lowe.
BODY-WEIGHT OF MEN RELATED TO STATURE, AGE, AND SOCIAL STATUS. WEIGHT OF SCOTSMEN MEASURED IN 1941. E. M. B. Clements and Kathleen G. Pickett.
CHEST GIRTH OF MEN RELATED TO STATURE, AGE, BODY-WEIGHT, AND SOCIAL STATUS. CHEST GIRTH OF SCOTSMEN MEASURED IN 1941. E. M. B. Clements and Kathleen G. Pickett.
HETEROSPECIFIC PREGNANCY. J. M. Johnstone.
SEX RATIO AND THE ABO BLOOD GROUP SYSTEM. J. M. Johnstone.
SOCIAL CLASS VARIATIONS IN MORTALITY. W. P. D. Logan.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Black.**—On June 24, 1954, at Aberdeen Maternity Hospital, to Dr. Margaret Caie, wife of J. Knowles Black, M.B., B.Ch., D.A., of "High Bury," Grafton Drive, Upton, Wirral, Cheshire, a son—Stephen Farquharson.
**FitzGerald.**—On July 20, 1954, to Ita (formerly MacAuliffe), M.B., B.Ch., B.A.O., wife of Maurice A. FitzGerald, M.B., B.Ch., B.A.O., D.M.R., 10, Upper Maze Hill, St. Leonards-on-Sea, Sussex, a brother for James and Mary.
**Jones.**—On July 28, 1954, at Farnborough Hospital, Kent, to Dr. C. Margaret Watt, wife of Dr. David C. B. Jones, a son—Charles Richard.

### DEATHS

**Freeth.**—On July 26, 1954, at "Surrey Cottage," Porlock, Somerset, Harold Freeth, M.D., aged 75.
**Walters.**—On July 26, 1954, Alexander Radclyffe Walters, M.R.C.S., L.R.C.P., J.P., of 1, Alders Court, Reigate, Surrey, aged 86.

# Any Questions?

*Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.*

### Encephalopathy after T.A.B.

**Q.**—*Recently a Chinese child of 6 years was given a first inoculation of 0.2 ml. T.A.B. vaccine. The child became feverish that evening with a temperature of 106° F. (41.1 C.), and was admitted to hospital, where she died two days later. The body was not available for post-mortem examination. There appeared to be no physical abnormalities in the various systems except for mild leucocytosis (10,400). The cause of death was attributed to "hyperpyrexia due to T.A.B. inoculation." About 400 to 500 children were inoculated at the same time and place, and none, except this child, became ill. What is your expert's opinion of this case?*

**A.**—In the absence of a necropsy, it is impossible to decide whether death was due to the vaccine or to some unsuspected intercurrent condition. The illness may have been an "encephalopathy," analogous to those reported after injections of pertussis vaccine in the U.S.A. by Toomey[1] and in this country by Anderson and Morris.[2] Such attacks are often associated with pyrexial illnesses, and may prove fatal. Encephalitic symptoms have also followed, though very rarely, smallpox vaccination and rabies or T.A.B. inoculations. The pathogenesis is unknown. Possible causes include the activation of a latent virus by the vaccine, or a cerebral vascular accident, associated with thrombosis of small cerebral vessels. Leakage from the inoculation site into a small vein would explain the latter mishap.

REFERENCES
[1] *J. Amer. med. Ass.*, 1949, 139, 448.
[2] *Lancet*, 1950, 1, 537.

### Inheritance of Otosclerosis and Congenital Dislocation of the Hip

**Q.**—*My patient is a woman of 28 who has early otosclerosis. She wishes to marry her first cousin. A mutual aunt became deaf at an early age with no previous history of otitis media. My patient's paternal grandfather was very deaf, but it is not known under what circumstances the deafness started. Also, her fiancé's brother's daughter has congenital dislocation of the hip. What should I tell this couple about the chances of their offspring developing otosclerosis or congenital dislocation of the hip?*

**A.**—This is a very difficult question, as the genetics of both conditions are obscure. Then there is the complication of the projected cousin marriage. With congenital dislocation of the hip the most favoured explanation is that a dominant gene is involved, though only a rather small proportion of the bearers of the gene are actually affected. The apparently normal bearers may often, however, show on *x*-ray examination an acetabulum which is shallower or flatter than in the normal hip. An alternative explanation which has been put forward tentatively is that the shallow acetabulum may be due to one dose of the gene and the deformity itself to the double dose. If the fiancé's brother's child is the only instance in the whole family group, the likelihood of a child of the projected marriage being affected is probably quite small.

The favoured explanation in otosclerosis is again a dominant gene manifested by some bearers only. It is likely that there are non-hereditary or sporadic cases also, but that does not arise here, as there is a definite family history. To add to the difficulty some pedigrees suggest recessive

inheritance. There is certainly a risk that this woman may transmit deafness to a child, though probably it is not a very large chance. There may be some slighter risk that her fiancé also might transmit. On the dominant view (which is the likely one here) the two independent risks are additive, but not directly because of the blood relationship—i.e., the risk would be the same with unrelated people who had the same family histories of deafness as the couple described. I feel that it is desirable to get a much fuller family history. One would like to know as much as possible about the unaffected members of the families as well, with their ages, and an assessment of the evidence of their freedom from deafness. A better estimate of the chances should then be possible.

### Hyperextension of the Neck During Tonsillectomy

**Q.**—*Are there any dangers associated with the hyperextension of the neck of the patient whilst a tonsillectomy is performed under general anaesthesia?*

**A.**—Although tonsillectomy is probably the most frequently performed surgical operation, cases of dangerous complications due to hyperextension of the neck are very rarely reported. One, however, was reported a few years ago which resulted in paraplegia.

Conditions under which hypertension of the neck might occur would be too large a sandbag under the shoulders of the supine patient on the operating table, combined with further extension of the head on the neck by pulling on the handle of the Boyle–Davis gag. Only a very flat sandbag or preferably a folded towel should be placed under the shoulders, and some surgeons prefer not to use anything at all under the shoulders. If the Boyle–Davis gag is kept in position by a mechanical jack rather than the anaesthetist's or an assistant's hand, then overextension can be avoided. It is probably wiser not to turn the patient on his side when the Boyle–Davis gag is still in position, because in doing so the hand-piece of the gag can be pulled upon in such a way as to produce hyperextension.

### Scrotal Pruritus

**Q.**—*What treatment is advised for chronic and intractable pruritus of the scrotum, present for the last ten years? Many remedies have been tried without success. The skin around the root of the penis is thickened and cornified. The other parts of the scrotum show chronic inflammatory changes but no thickening. Itching is intense and the consequent scratching aggravates the condition. The skin on the inner side of the thighs is dry, pigmented, and itchy. There is no sugar in the urine.*

**A.**—The affection is probably a neurodermatitis of the lichen simplex type. Basically the problem may call for some attention psychologically, but so far as local measures are concerned relief is likely to be afforded by painting with 1% gentian violet lotion or the use of one of the following pastes: coal tar (20 gr.—1.3 g.), zinc oxide (180 gr.—11.7 g.), yellow petroleum jelly to one ounce (31 g.); or, podophyllin (¼ to ½ gr.—16 to 32 mg.), zinc paste to one ounce. Probably small doses of phenobarbitone internally would also help.

### Recurrent Folliculitis

**Q.**—*What treatment is advised for obstinate staphylococcal folliculitis around the buttocks and between the thighs of a middle-aged man? In the last eight months I have tried, without success, local antiseptics, oral penicillin (500,000 units t.d.s.) and staphylococcal vaccoid. The urine is normal and there is no obvious septic foci.*

**A.**—Recurrent folliculitis may depend upon repeated sources of infection or upon continued reinfection of the skin from one furuncle to another. The localization of folliculitis about the buttocks may indicate defective personal hygiene, and it is suggested that this patient should be instructed carefully to wash the area with soap and water after defaecation. With regard to the local spread of infection, a common mistake is in making dressings too small. With a single furuncle it is advisable to have antiseptic dressings at least 4 in. (10 cm.) across, and if a wide area such as the buttocks and groins is affected it will probably be advisable to apply a dressing as large in proportion as an infant's diaper. This should be made with gauze and impregnated with 1:2,000 mercury perchloride and continued so long as active furuncles, discharging pus, are present.

Once active furuncles have ceased to appear it may be sufficient if the whole area is swabbed twice daily with 50% spirit and allowed to dry, and then liberally covered with talcum powder.

### Cortisone for Alopecia

**Q.**—*A patient tells me that cortisone is effective in the treatment of alopecia. What is the truth of this claim?*

**A.**—There is no convincing evidence that cortisone is useful in alopecia, though there is evidence that in many cases it has been of no use. There is sometimes a response while the patient is on treatment, but almost invariably relapse when it is stopped.

### Antispasmodics in Disseminated Sclerosis

**Q.**—*Are the new antispasmodics such as diethazine hydrochloride ("diparcol"), which are of use in paralysis agitans, of any value in the relief of the muscle spasms and rigidity of disseminated sclerosis?*

**A.**—I do not know of a carefully controlled study on this subject, but my personal experience is that the new antispasmodics which are often helpful in reducing the extrapyramidal rigidity of Parkinson's disease are of little value in reducing the pyramidal spasticity of disseminated sclerosis.

### Gold Therapy and Psychotic Changes

**Q.**—*Are psychotic changes a recognized complication of intensive gold therapy? I have a patient of 68 who was given heavy doses of gold injections in 1949, and is now suffering from restlessness, wandering, severe mental deterioration, and disorientation in time.*

**A.**—There are no published reports of psychotic changes as complications of intensive gold therapy. In spite of other metals causing such changes, gold has not so far been implicated.

The particular patient quoted would be unlikely now to have any complications from gold if it was given in 1949, because the longest recorded time before the metal was finally eliminated is 15 months.

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**Refresher Course Books.**—The first two volumes of collected articles from the Refresher Course for General Practitioners published in the *Journal* are now available. The first volume contains 55 articles and the second 60. Each article has been revised by its author. Copies of both volumes may be obtained, price 25s. (postage 1s.) each, direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers. The second book of "Any Questions?" is also available, price 7s. 6d. (postage 6d.).

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